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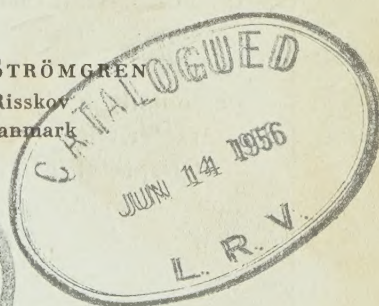
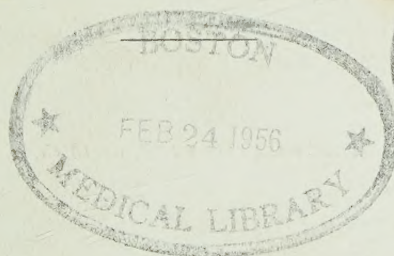
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EJNAR MUNKSGAARD · KØBENHAVN 1955

H. C. RUMKE

Problems in the Field of Neurosis and Psychotherapy

This book contains a series of five lectures held in Denmark (1950) and in the United States of America (November, 1951). The first lecture is a prelude in which the author attempts to reveal the frame of mind in which the lectures were conceived. The following points are at issue: The significance of the clinic in psychiatric investigation; the danger of systems; the replacing of the idea of causality by the idea of "conditions"; the principle of Hughlings Jackson; scope and limits of psychogenesis; dynamic and static interpretation in psychiatry; certainties and uncertainties in depth psychology. The author points out that neurosis is not a *morbis sui generis* but a syndrome. He tries to see how psychological and neurophysiological conditions are integrated. The significance of the conception of neurosis of the ascending and descending curve of life introduces the themes of lecture III (what factors determine an optimal psychic development) and lecture IV (phases of life and psychotherapy). In lecture V the author gives his opinion on what is changeable in the personality and what is not. At the end he describes some of the characteristics of the psychiatrist.

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SOME SOMATIC PROBLEMS IN SCHIZOPHRENIA

By

ARILD FAURBYE

INTRODUCTION

We have now got so far in somatic research of schizophrenia that we are on firm ground in several places. In what follows an account will be given of some investigations which by being collocated will throw new light on the somatic basis of schizophrenia, so that fruitful fields for continued research may appear.

The subjects of these investigations are the autonomic nervous system, the adrenal cortex, the function of the thyroid gland, and certain enzymatic processes.

A flood of somatic investigations into schizophrenia have been made; so we must desist from any attempt at making a full survey. One of the greatest difficulties at the evaluation of such investigations is the great variation of psychiatric nomenclature, the concept of schizophrenia in general being much wider in Britain and especially in U.S.A. than in this country, a fact which must therefore always be kept in mind.

There are also valuable investigations outside the field chosen here, thus it is possible in schizophrenia to demonstrate the occurrence of changes of the testes, the parathyroid glands, the liver, the circulation, etc., but it would take us too far to go into all these details.

SCHIZOPHRENIA DIAGNOSTICS AND SOMATIC TYPES

As mentioned in the Introduction schizophrenia is diagnosed widely differently in different countries, as there are no pathognomonic symptoms. Hence it may be difficult to compare investigations from different countries and centres of research. In research the limits should generally be fixed narrowly in order to obtain as homogeneous cases

as possible. If the limits are too wide, there is a risk that the material will include cases with an uncertain and varying etiology and pathogenesis.

According to the generally accepted points of view in this country there is a common hereditary factor whose presence is necessary for the development of schizophrenia. In some cases this hereditary factor may be sufficient to make the disease manifest itself, but in many cases one or more releasing factors are needed to provoke the disease. Febrile diseases, exhaustion, want of sleep, severe psychical traumata, etc., may be seen to provoke schizophrenia; but when the disease has broken out, it seems to be the bodily constitution which to a wide extent determines the further course of the disease.

Endocrine factors influence the ease with which schizophrenia arises; this appears from the fact that there is an accumulation of cases which start during puberty and the climacterium. The bodily constitution, including endocrine conditions, is on the whole of essential importance both to the normal psyche and to the rise and course of psychoses, as has especially been pointed out by *Kretschmer* and *Mauz*. Schizophrenia, as is well-known, is especially correlated to the leptosomatic type of body build, and the manic-depressive psychosis to the pyknic type. If schizophrenia occurs in a markedly leptosomatic person, the disease will generally break out during puberty or the early youth, the course of the disease being gradual to a final stage of deterioration of the personality. If the type of body build is not so markedly leptosomatic, but displays some pyknic traits, this will often clinically be reflected in the fact that the disease manifests itself at a later time, and that the course is not gradual, but that there are periods of remission, and furthermore there may be catatonic symptoms (stupor and exaltation). If schizophrenia appears in a pyknic person, it will often start about the age of 40 or later; its course is slow; clinically these cases are generally dominated by delusions, and in many cases there will be no deterioration of the personality, as is seen in the hebephrenic types which start in youth in leptosomatic persons. Correspondingly manic-depressive psychosis in pyknics takes an intermittent course, while in the leptosomatic patient it has tendency towards being chronic without periods of remission.

This shows that the various types of body build have a widely different value as a substratum of psychoses. In this connexion it is very interesting that *Kline et al.* have been able to show that many biological factors are different in the various types of body build. This applies to albumin and globulin in the blood, non-protein nitrogen, cholesterol, the blood picture, etc.

Periodic catatonia, which *Gjessing* (1932-53) has studied so thoroughly, is a schizophrenic psychosis in a more or less pyknic person. We may see here quite regular fluctuations between phases of "stupor" and phases of "awareness", but if intercurrent bodily disorders appear, e.g. focal infection, the rhythm in the psychosis is disturbed and the phases become of different intensity and duration. If catatonic schizophrenia appears in a leptosomatic person, we generally do not see any periodicity or rhythmical changes in the condition. Instead there may be a prolonged or continuous state of stupor or exaltation without distinct rhythmical fluctuations, but perhaps with some irregular variation in the condition, perhaps because of focal infection, from which leptosomatic patients are inclined to suffer.

When trying to appraise the investigations mentioned in what follows we should therefore allow for the authors' diagnostic points of view, and it should also be considered that many biological factors vary with the somatic type.

The Autonomic Nervous System.

Changes in the autonomic nervous system are often described in schizophrenia. *Langfeldt* already in 1926 advanced the theory that dysregulation of the autonomic centres in the diencephalon form an integral part of the pathogenesis of schizophrenia. Similar points of view have been advanced from various quarters, the physiologist *Gellhorn* even being of opinion that reduced function of the hypothalamic sympathetic centres is a crucial point in the schizophrenic disorder.

Funkenstein, Greenblatt & Solomon in a number of works have advocated a pharmacological testing of the tonus of the autonomic nervous system. This has been attempted numerous times previously, but these recent investigations do not seem convincing either. *Solomon, Darrow & Blaurock* find that the power of sympathetic reaction is improved alongside of clinical improvement in schizophrenic patients who are treated with insulin coma and metrazol shock. *Jahn* found similar results after insulin coma treatment.

The occurrence of vagotonia in schizophrenics can be considered certain, as vagotonia has been shown to occur by authors, who use widely different criteria for the diagnoses of schizophrenia; but it is uncertain how frequently vagotonia occurs in schizophrenia and whether it is connected with any of the clinical subtypes, or whether it depends on the somatic type rather than the psychical picture.

The investigation which delves most deeply in this field is *Gjessing's* (1932 a and b) demonstration of vagotonia as a component of the

retention syndrome in periodic catatonia. In this connexion it should especially be noted that vagotonia occurs as a single component in a larger complex of biological factors and connected with a definite psychical symptom—stupor. This is a useful demonstration of the fact that the tonus of the autonomic nervous system cannot be regarded as an isolated phenomenon, which many authors seem to forget. The question of vagotonia also depends on the way in which this concept is defined and of the methods with which it is diagnosed.

We may agree with *Langfeldt* and *Gellhorn* in the view that in schizophrenia there is dysregulation in the hypothalamic autonomic centres, but the available investigations hardly warrant considering these central autonomic disturbances as a crucial point in the pathogenesis of schizophrenia; for this the disturbances are too unspecific.

In connexion with the theory of a disturbance in the autonomic centres in the hypothalamus in cases of schizophrenia it is interesting to consider the pattern of emotions in schizophrenia. The normal mechanism of the emotions is that some experience affects the senses, a stimulus reaches the hypothalamus, from where impulses are passed on to the periphery through the sympathetic and parasympathetic nervous system (*Cannon*). This results in adrenalin and insulin secretion and rise of the other well-known somatic attributes to emotions, but besides, impulses pass from the hypothalamic centres to the cortex cerebri, through which the consciousness of the experience obtains its emotional component: "the emotion is experienced as an emotion".

Now, changes in emotional life is one of the characteristic traits of schizophrenia; there appears an emotional deterioration or distortion of mood so that experiences which would give rise to emotions in psychically healthy persons do not make any impression in schizophrenics, who, on the other hand, may react emotionally to quite trifling and imperceptible matters. It is often seen that the death of a spouse or a child does not make any impression upon a schizophrenic; it is as if this experience has not got any emotional tone in a schizophrenic. The same patient perhaps may fly into a temper at a trifle to which other people would not react.

We must then assume that in the case of schizophrenia there is often a disturbance in the autonomic centres of the hypothalamus which can manifest itself both in disturbance of centripetal impulses (the emotional tone) in the case of emotions and in disturbance of the centrifugal impulses (vagotonia). But it is uncertain how much these disturbances mean and how frequent they occur and what other biological factors they are connected with.

The Intermediary Metabolism.

In recent times some anomalies in the intermediary metabolism have been shown to occur in psychoses, presumably due to disturbances in the enzymatic processes which give rise to transformation of the intermediary metabolic products. It is uncertain how this can be connected with the endocrine disturbances mentioned in what follows; but as the hormones affect the enzymatic processes in the tissues, and as the hormonal changes themselves are perhaps due to enzymatic disturbances, it is tempting to imagine that there is a certain connexion.

Munkvad in schizophrenics in the active phase of the disease has found pronouncedly low glutamic acid values and often increased glutamine in plasma. In cases of recurrent schizophrenia there were pronouncedly low glutamic acid values in the bad phases, while the values became normal in good phases in the cases in which the disease had existed for at least ten years. In recent cases the glutamic acid rarely reaches normal values in the good phases. In the case of electro-shock treatment there was an increase in glutamic acid immediately in connexion with the treatment. The increase was highest with low values and might be up to ten times the original value. The increase soon subsides. Low glutamic acid values may also occur in manic depressive psychoses. A pathological course of enzymatic processes in the transformation of glutamic acid and glutamine might explain the anomalies, but so far no satisfactory explanation can be given.

Buscaino & Rapisarda have found increased alpha-ketoglutaric acid values in catatonic schizophrenia, but there was a wide range of their values and a defective control material.

The Adrenal Cortex.

The adrenal cortex is regulated by the hypothalamic pituitary system. If adrenal cortex hormones (ACH) are missing in the blood, the hypothalamus will stimulate the pituitary to produce a hormone (ACTH) stimulating the adrenal cortex, which then makes the adrenal cortex secrete ACH, which by way of the circulating blood checks the hypothalamus pituitary system so that less ACTH is produced. In this way the pituitary gland and the adrenal cortex hold each other in check in a state of equilibrium. ACH is used in the peripheral tissues during metabolism; if much is used, there will be less ACH to check the pituitary gland and the system adjusts itself to a high level while, when at rest, it adjusts itself to a low level (*Sayers & Sayers*).

It has been possible to isolate 35 different ACH's. This is not to

say that the adrenal cortex produces 35 hormones. It must be assumed that the adrenal cortex synthesizes a single hormone, which then is decomposed and changed through a number of different stages, and that each of these products of transformation has its definite biological effect. Some have a more or less androgenic effect, others affect the carbohydrate and the protein metabolism, and others again affect the water and salt metabolism. If adrenal glands are perfused with cholesterol, which is the parent substance of ACH, we shall get quite a series of hormonal substances in the perfusion fluid, which shows that the transformation or decomposition of the primary ACH begins in the adrenal cortex itself, before the hormone enters the circulating blood, or that some hormonal substances escape into the circulating blood before they have been finished and become the proper hormone.

If a person who has had both adrenal glands removed is kept alive by means of cortisone, the same varied amount of ACH will be found in the urine as in persons with intact adrenal glands, which shows that the transformation of ACH also takes place in the peripheral tissues. Both in the case of deficiency in ACH (Addison's disease) and in the case of hyperfunction of the adrenal glands we regularly find psychical disturbances, partly as isolated psychical symptoms, but also frequently as psychoses. These complaints generally disappear when the hormonal status is restored. Thus, there must be an optimum for the influence of the ACH on the function of the brain, as psychical disturbances arise both when there is too little and when there is too much ACH. So far the influence of possible abnormal AC-steroids upon the function of the brain cannot be determined.

Hoagland (1951, 1953), *Mittelman et al.* (1952), *Romanoff* (1953), *Hoagland et al.* (1952), *Hemphill & Reiss* (1950), *Reiss* (1951, 1952 a and b, 1953), *Faurbye et al.* (1951) have demonstrated the occurrence of a relative adrenal cortex insufficiency in schizophrenia, both under standard conditions (*Hoagland* (1953)) and under stress (*Faurbye et al.* (1951) and *Hoagland* (1953)).

Hoagland's last table (1953) (he has the largest material and the one investigated best) shows that schizophrenics under standard conditions, i.e. fasting in the morning, secrete more 17-KS and less cortin in the urine than normal control persons. The difference is statistically certain. There is great overlapping, but the difference is statistically significant in a sufficiently large material. Thus there is here a displacement from one kind of ACH to another, perhaps because of some disturbance in the enzymatic processes which transform (decompose) the ACH. As there are 35 or more stages, there is nothing strange in the fact that something may go wrong. In congenital AC hyperplasia

(*Gordan*) the pathogenesis seems to be that there is a stop in the processes of decomposition so that no hydrocortisone is produced, which is the substance or one of the substances that check the ACTH production of the pituitary gland. When this substance is missing, the pituitary gland will continue producing ACTH, which then provokes an AC hyperplasia. Clinically it is then possible to observe the remarkable fact that virilism appears as a sign of a surplus of androgenes, and at the same time Addison symptoms, i.e. AC insufficiency as a sign of cortin deficiency.

It is then imaginable that there is a similar enzymatic disturbance in schizophrenia, in which, however, there is no complete stop, but a certain restraint somewhere in the decomposition process. This might explain *Hoagland's* finding (1953), increased secretion of 17-KS and reduced secretion of cortin. Correspondingly *Lohse & Bjarnhjedinson* have virilism in 60 per cent. of schizophrenic women, which suggests a surplus of androgenic AC hormones (= 17 KS). The poor stress reaction in schizophrenics might perhaps be connected with a slight production of cortin (*Faurbye et al.*).

Other signs of disturbance in the decomposition or transformation of ACH in schizophrenics have also been found.

Mittelman et al. thus in *Hoagland's* laboratory have found that secretion of beta-KS was greater in schizophrenics than in normal persons, i.e. there was a shifting from alpha-KS to beta-KS in schizophrenics. We are at present testing this statement at St. Hans Hospital, but in our preliminary results we have not been able to confirm it. Some investigations by *Louise Romanoff* in *Hoagland's* laboratory seem to be more significant. Together with various collaborators she has made chromatographic analyses of steroids in urine from normal and schizophrenic persons. The preliminary results, which have been mentioned by *Hoagland*, are based on analysis of 1 pool of urine from 4 normal men and 1 pool of urine from 4 normal women, furthermore individual samples of urine from 6 male schizophrenics and from 2 female schizophrenics who had had their adrenal glands removed because of mammary cancer and were kept alive by means of cortisone.

By the chromatography 35 steroid substances were isolated. 1 substance was found in all the schizophrenics, but not in any of the 2 normal pools, and 1 substance was found in the 2 normal pools, but not in any of the 8 schizophrenics. 29 substances were found in all the samples, but there were various mutual displacements.

The 2 women suffering from schizophrenia who had had their adrenal glands removed are particularly interesting. They were examined both before and after their total adrenalectomy, and it ap-

peared that after the operation, while they were kept alive with cortisone, they secreted practically the same amount of steroids as before the operation. This shows that the transformation of steroids takes place in the peripheral tissues. But the investigations have not yet been finished and with the limited material available it is not possible to make any final evaluation.

The reduced adrenal cortex reaction to stress in schizophrenics has been demonstrated from several quarters and must be considered as certain. The displacements of the AC steroids mentioned by *Hoagland* and his collaborators seem very probable, since, as mentioned above, they are supported by clinical experiences. The reason for the displacements might be a disturbance in the enzymatic processes which give rise to decomposition of the steroids. This is of the greater interest as we also in other spheres find conditions which indicate enzymatic disturbances in schizophrenia, as will be mentioned in what follows.

The Thyroid Gland.

The thyroid gland is regulated by the hypothalamus-pituitary system. If thyroid hormone (TH) is missing in the blood, the hypothalamus stimulates the pituitary to produce a thyroid-stimulating hormone (TSH), which then makes the thyroid gland secrete TH, which by way of the circulating blood checks the production of TSH.

According to *Roche, Lissitzky & Michel* the TH-formation takes place by the thyroid gland absorbing iodide, which is oxidized to iodine, and this is bound to amino acids in thyroglobulin, which is found in the thyroid gland. By this means iodothyroglobulin is developed. This is, however, a giant molecule with a molecular weight of about 700,000. It is so large that it cannot pass into the circulating blood, and so it must be split up into iodic polypeptides. In the iodothyroglobulin there are various iodized amino acids, but in the blood there is practically only tetra-iodothyronin (thyroxin) and tri-iodothyronin.

Tri-iodothyronin has been shown to occur in blood by *Gross & Pitt-Rivers* by chromatography and by *Roche & Michel* (cit. *Harington*). It is five times as active as thyroxin and by *Pitt-Rivers* is regarded as the TH proper, as she assumes that the thyroxin in the peripheral tissues is transformed into tri-iodothyronin, which then affects the cell metabolism.

The splitting up of the iodothyroglobulin in the thyroid gland takes place continually, but is regulated and speeded up by TSH (*Roche, Lissitzky & Michel*). The effect of TSH, for that matter, is hardly completely elucidated. As described by *Iversen* TSH is a protein substance.

If it is injected, hyperplasia of the thyroid gland and increased formation of TH with increase of the basal metabolism will arise, but the effect is transient, in a few days an antihormone develops which stops the effect. It has been tried to utilize this antihormone for treatment of hyperthyroidism, but nothing worth mentioning has come of it and it is still uncertain whether antithyroidin is of any importance in the human clinic. But there are some early investigations by *Caulert, Aron & Stahl* which show the remarkable fact that in some cases of myxedema there is an increased amount of TSH in blood and urine, and in the case of hyperthyroidism a reduced amount, which would seem to indicate the occurrence in the blood of a substance which neutralizes the effect of TSH (antihormone?). The occurrence of substances which check hormonal effects is fairly common; see the discussion in *Pincus* (1952), *Harington* (1953), and *Mansfeld* (1943).

TH has a direct effect upon nervous tissue by increasing the irritability. We all know the psychical picture in myxedema and the psychoses in thyrotoxicosis. TH increases the anaerobic oxidation in the tissue cells and in this way brings about an increased consumption of oxygen, and in general it is possible to use the consumption of oxygen under basal circumstances as a measure of the activity of the thyroid gland, but TH is not the only factor determinative of the oxygen consumption. Furthermore it may be difficult or impossible to provide basal circumstances or to ascertain whether they are present or not. The use of the oxygen consumption as a measure of the thyroid function therefore involves a considerable uncertainty and a possibility of error of judgment. Thus we should not identify basal metabolism (oxygen consumption) with thyroid function. It is e.g. possible to find increased metabolism and normal thyroid function in neuroses or normal thyroid function and reduced metabolism (consumption of oxygen) e.g. in cases of hypogonadism or hypothalamic disorders, etc.

The amount in the blood of protein bound iodine (PBI) generally corresponds to the amount of circulating TH and therefore often is a better measure of the thyroid function than the basal metabolism as described by *Friis* (1954a and b), perhaps especially in the case of reduced values; but the methods of analysis are difficult and time-consuming. With radioactive iodine it is possible to determine the absorption of iodine in the thyroid gland and in this way to obtain a certain standard for the function; but the methods to be used are not completely clarified and the results are difficult to appraise.

In the case of *schizophrenia* various deviations of the thyroid function from the normal have been shown to occur, some of the principal ones being the following:

Lingjærde in 1933 examined the basal metabolism (the consumption of oxygen) in 118 schizophrenics:

59 (50 %) metabolism 90–112 %
 43 (36 %) metabolism 80– 90 %
 16 (14 %) metabolism 70– 80 %

Lingjærde then attempted to raise the metabolism with thyroidin. Indeed, there were many who before him had found a low consumption of oxygen and instituted treatment with thyroidin without any result; but the significant fact was that he used very large doses so that the metabolism rose to about 110 per cent. with a pulse of 90–100, and that he continued doing so far a long period, up to six months to one year. About half of the 50 schizophrenics who were treated improved considerably or were cured; especially cases with stupor and apathy improved. The dose was thyroidin tablets (dried substance of thyroid gland) corresponding to 0.3–2.1 gramme fresh gland (about 0.1–0.7 mg thyroxin) per day.

Hoskins, who presumably has the greatest material, in 1932 reported the result of examinations of 215 schizophrenics. By very careful examinations with up to 15 measurements of basal metabolism in each patient he found for the whole group an average basal metabolism of 81 per cent. calculated from the lowest value in each patient. 10 per cent. of them besides a reduced consumption of oxygen showed other signs of hypothyroidism. In these patients the psychical condition improved by administration of thyroidin; but this preparation did not help in the others with a reduced consumption of oxygen. *Cohen* (1939) *Cohen & Fierman* (1938), *Cohen & Hoskins* (1939) showed that large doses of thyroidin (50 grammes dried gland or 5 mg thyroxin intravenously), which ought to produce violent hypermetabolism, had only a slight effect.

Hoskins (1946) calls attention to the fact that the symptoms of schizophrenia very much resemble the psychical symptoms seen in the case of oxygen deficiency, and on the basis of his findings in schizophrenics of (1) normal oxygen pressure in the blood, (2) reduced consumption of oxygen (basal metabolism), and (3) imperfect effect of thyroidin, he concludes that there must be a *defective enzymatic system in the tissues of schizophrenics*, which causes that the cells cannot utilize the oxygen found in the blood. Instead *oxygen deficiency arises in the cerebral cells, through which the psychical symptoms arise.*

Freeman found that schizophrenics react to alpha-dinitrophenol less than normal persons.

Bowman et al. have investigated the absorption of radioactive iodine in the thyroid gland, the basal metabolism, the amount of iodine bound to protein, and the amount of cholesterol in serum in various psychoses. Most values ranged within the normal, but in schizophrenics there was a tendency towards combination of high absorption of iodine suggesting great activity of the thyroid gland and a low basal metabolism suggesting slight activity of the thyroid gland. In the authors' opinion the reason for this constellation may be a wrongly composed TH, or the fact that the tissues do not consume the oxygen offered. The authors' diagnostics of schizophrenia seem rash, but otherwise their results correspond very well to those of *Hoskins* and others.

Hemphill & Reiss (1950) in Bristol have in a number of publications (*Reiss* 1951, 1952 a and b, 1953) studied the function of the thyroid gland, especially fastening upon its relation to the adrenal cortex and other endocrine glands and upon the sensitivity of the tissues to hormones. They have examined 600 psychotic patients with radioactive iodine and basal metabolism, but state that they could not find any correlation between the function of the thyroid gland and the various disorders, even though they found many cases of hypo- and hyperthyroidism.

As stated by *Reiss* (1951) they did not either always find correspondence between the iodine method and the basal metabolism. In one group the iodine method showed increased function of the thyroid gland simultaneously with normal or reduced basal metabolism. In such cases they suppose that the tissues have a reduced sensitivity to TH, and that the increased function of the thyroid gland may be an attempt at compensation.

Reiss (1952 b) states that peripheral hyposensitivity to hormones is found in schizophrenics. This applies to AC hormones as well as thyroidin and insulin. In the case of TH it thus appears as normal or increased activity of the thyroid gland determined with radioactive iodine combined with reduced basal metabolism. Furthermore *Reiss* states that he is able to increase the sensitivity to testosterone by administering vasodilatory substances—nicotine acid and priscol (benzyl-imidazoline). *Reiss* (1952 b, 1953) discusses another very important question, viz. the relation between the various endocrine glands, and emphasizes the importance of maintaining *the right hormonal equilibrium*; it is not sufficient to study one hormone at a time. *Reiss* (1953) states that there is antagonism between the thyroid gland and the adrenal cortex and gives several examples from psychoses not especially

described, in which in the psychotic phase there was an increased function of the thyroid gland (determined with radioactive iodine) simultaneously with a reduced function of the adrenal cortex (determined by secretion of 17-KS and cortin for 24 hours). In the case of treatment or spontaneous improvement the function of the thyroid gland decreased, while that of the adrenal gland increased. In a case of puerperal depression there was thus an increased activity of the thyroid gland and at the same time reduced secretion of 17-KS and cortin. In the case of spontaneous improvement the iodine index dropped and the secretion of 17-KS and cortin increased. In another patient there was no spontaneous improvement, but by treatment with testosterone + estrone the same hormonal changes and psychical improvement occurred. In other cases testosterone treatment did not produce any of the hormonal changes mentioned nor any psychical improvement. In *Reiss's* opinion the reason for this must be that the testosterone has been destroyed in the tissues in the same way as the endogenously formed steroid hormones, and he assumes that such a destruction might be the cause of the poor excretion in the urine of endogenous hormones, which perhaps are actually produced to a normal extent.

Gjessing (1932 a and b, 1936, 1939, 1953 a, b, c, and d) has made fundamentally important investigations into *periodic catatonia*, a schizophrenic form of psychosis characterized by alternation between periods with stupor (or exaltation) and intervallary periods during which the patient is relatively "aware". It appeared that various biological factors varied in time with the psychical fluctuations.

He found a regular rhythmical fluctuation in the nitrogen balance. In normal persons variations in the administration of nitrogen are very quickly equalized; but in periodic catatonia *Gjessing* found periods with nitrogen retention, during which the patients day after day retained fairly the same amount of nitrogen. When for some weeks an average of 15–25 g N was retained, the balance became negative: the patient began excreting more nitrogen than corresponded to the administration of N, and when the whole amount of N retained was excreted, the patient again began to retain N.

The fluctuations in the psychical condition and in the nitrogen balance bear a definite proportion to one another. The change from the state of "awareness" to stupor takes place abruptly, often in a few hours; the stupor at a maximum lasts for a few days, then slowly relaxes in order finally rather evenly to slide into the state of "awareness"

The abrupt change into stupor in some patients sets in when the

retention of nitrogen has reached its maximum, in others in the middle of the evacuation of N, and in others again at the minimum of the N curve. In the same patient the change always sets in at the same point of the N curve. It also appeared that *in the intervallary phase of "awareness"* there was a reduced consumption of oxygen (basal metabolism) and a moderate vagotonic adjustment of the autonomic nervous system (comparatively slow pulse, low blood pressure, low leukocytic values with relative lymphocytosis). In *the stuporous phase*, on the other hand, there were increased basal metabolism and sympathicotonia. The psychical fluctuations, the basal metabolism, and the tonus of the autonomic nervous system always very closely accompany each other, while, as mentioned above, the relation to the nitrogen balance may be different.

Gjessing also made hyperhydration tests during the various phases. 1500 ml water was given in the morning when the patient was fasting, the diuresis then being measured during the following four hours. Very great variations appeared. In the intervallary phase of "awareness" in which nitrogen is retained, the excretion of water decreases under the hyperhydration test and may even drop to 2–300 ml at the end of this phase, i.e. the water-binding capacity of the tissues increases when nitrogen is retained: the tissues retain the water. But when the nitrogen evacuation and the stupor starts, there is at once a greater excretion of urine at the test; the diuresis may increase as far as 1500–1700 ml at the test during the days when the stupor is replaced by the state of "awareness". The spontaneous diuresis shows the same tendency towards variation, but the results are not so distinct.

The excretion of salt in the urine (determined by gravimetry) during the hyperhydration test shows the same tendency as the diuresis, but the curve has an independent course.

Gjessing ascribes the fluctuations in the nitrogen equilibrium to the function of the thyroid gland. He states that in the intervallary phase, when the metabolism is reduced, there are slight signs of myxedema, and inversely during stupor slight signs of hyperthyroidism (slight exophthalmus, high frequency of the pulse, tremor manuum, and increased sensitivity to oxygen deficiency) besides the increased basal metabolism.

On the basis of this observation *Gjessing* began to treat cases of periodic catatonia with thyroidin. He gave a "thyroxin shock", i.e. 40–80 mg thyroxin injection intramuscularly for 8–10 days. The treatment was started at the peak of the curve of the nitrogen equilibrium, i.e. at the time when the nitrogen evacuation was supposed to start, thus obtaining an extra great nitrogen evacuation. Then thy-

roidin tablets were given continuously in such a dose that the basal metabolism was constantly about 110 per cent. In this way it was possible to prevent a fresh retention of nitrogen, and the psychical fluctuations also failed to appear: there were no fresh phases of stupor. In some cases there might be a single or a few psychical fluctuations, but in a greatly subdued form. Then the fluctuations ceased and in some time the intervallary state of "awareness" was gradually normalized.

Gornall et al. have studied the nitrogen balance in three cases of periodic catatonia (one with stupor and two with exaltation) for a couple of years. Their results were a corroboration of *Gjessing's* investigations. In the intervallary periods the patients had all a reduced basal metabolism, which increased abruptly at the commencement of stupor or exaltation, respectively. In one of patients iodine bound to protein was determined in the blood and was found to be normal simultaneously with reduced basal metabolism. The iodine showed no distinct increase when the basal metabolism increased at the commencement of stupor. In two patients the excretion of AC hormones was examined. One of them had a low excretion of 17-KS and normal excretion of cortin. After administration of ACTH there was a normal cortin reaction, but a defective 17-KS reaction. In the other patient the excretion of 17-KS increased immediately before the change into stupor. The reaction to ACTH was comparatively good, better for cortin than for 17-KS. In all the three patients treatment with thyroxin *ad modum Gjessing* brought about cease of the psychical fluctuations when the basal metabolism was stabilized about 110 per cent.

Mall communicates the result of thyroxin treatment *ad modum Gjessing* of 50 schizophrenics. Besides the very rare cases of periodic catatonia he tried to treat other schizophrenics who showed fluctuations or irregularities in the course of the disease. The disorders in question were:

- (1) periodically recurring paranoid-hallucinatory schizophrenia,
- (2) recurring hebephrenia,
- (3) catatonia with a tendency towards remission.

In 32 patients there was a favourable result. These were mainly pyknic and athletic types with a spontaneous tendency towards periodicity. 19 of these patients had previously undergone a more or less intensive electro-shock treatment without permanent effect, some patients also insulin-coma treatment. The observation period for the majority was two or three years. In 18 patients nothing came of the treatment. They were mainly leptosomatic, asthenic, and dysplastic types without any tendency towards remission. In a few of these patients

there were fluctuations in the nitrogen balance, but without any accompanying distinct psychical fluctuations.

Mall emphasizes that it is necessary to give the thyroxin shock at the time when the curve of nitrogen balance is at its maximum, as experience has shown that otherwise there will not be a sufficient evacuation of nitrogen, even with thyroxin doses of up to 100-120 mg.

Mall followed the excretion of non-protein N with one weekly determination instead of the curve of nitrogen balance, which in practice proved to give sufficient orientation to direct the treatment in most cases. The non-protein N curve takes a course exactly the reverse of that of the nitrogen balance.

As far as possible the patients were cleared of focal infection (the importance of this has also been emphasized by *Gjessing*). Focal infection affects the nitrogen balance so that this is difficult to evaluate, but it is not a counter-indication for the treatment. Removal of focal infection may in itself have a favourable effect upon psychoses.

During the thyroxin shock the patients often get rather worn out, with a pulse up to 160, pale and perspiring and with a rise in temperature. If the pulse becomes irregular or the patient otherwise gets too much worn out, the thyrotoxicosis may be stopped. Often it is sufficient to give a single injection of *water-soluble percorlen*, 25 mg intravenously, or up to three electro-shocks. In the interval after the thyroxin shock *Mall* often finds it expedient to give some electro-shocks (3-5) in order to consolidate the result. The administration of thyroidin is started about ten days after the cease of the thyroxin shock.

Danziger & Kindvall. In a material of 200 psychotic patients, mainly schizophrenics, but apparently quite unselected, thyroxin treatment for a long period was instituted. Well over half of 53 patients who were refractory to all other kinds of treatment, were cured or improved. The results were best in the cases in which it was possible to achieve a prolonged treatment. 28 out of 61 patients who were followed up after discharge had a relapse. In 26 of them this relapse set in 6-8 weeks after they had ceased taking the thyroidin prescribed on discharge. The authors could confirm *Gjessing's* particularly good results in cases of periodic catatonia. For that matter, the treatment was not used as a substitution therapy, but on the working hypothesis that also clinically normal metabolism should be increased to the uppermost limit of tolerance in order to stimulate the metabolism of the brain.

DISCUSSION

According to the available information it seems to be agreed that a reduced basal metabolism (consumption of oxygen) is often found in schizophrenia. The question then arises whether this reduction is due to thyroid insufficiency or it is due to some other cause, and what connexion it has with the mental disorder.

In myxedema the metabolism is easily and quickly corrected by means of thyroidin. Patients suffering from thyroid insufficiency react more vigorously to thyroidin than persons suffering from hypometabolism due to other causes and more strongly than persons with normal metabolism. *In the case of schizophrenia* the various writers agree that it is difficult to correct the reduction of the metabolism by means of thyroidin. According to *Hoskins* (1946), *Cohen* (1939), *Cohen & Fierman* (1938), *Cohen & Hoskins* (1939) it even seems to be more difficult to produce increase in the metabolism in schizophrenics than in persons with a normal metabolism. In schizophrenics it was necessary to use enormous doses, which would have given rise to severe intoxication in normal persons. Besides, *Hoskins* states that thyroidin only improved the psychical state in the cases when besides reduction of the metabolism there were other signs of thyroid insufficiency. This suggests that the reduction of metabolism in schizophrenia is not due to thyroid insufficiency. Furthermore, it may be stated that the metabolism in the case of myxedema generally is about 55–85 per cent, while in the case of extrathyroidal reduction of metabolism it is generally about 80–90 per cent, according to *Kirk & Kvorning*. In the case of schizophrenia the metabolism is generally about 80–90 per cent.

When *Bowman et al.* as well as *Reiss* and *Hemphill* and others in schizophrenics find signs of great activity of the thyroid gland (determined with radioactive iodine) combined with a low basal metabolism, this might seem to indicate that the thyroid gland functions well enough, but that the tissues do not react normally to TH. Thus there is every probability that the reduction of oxygen consumption in schizophrenia is of an extrathyroidal nature.

In the case of periodic catatonia there is the special feature that the basal metabolism has been shown to be only a component of a syndrome and varies together with various other factors. *Gjessing* is of opinion that these fluctuations in the metabolism are due to variations in the function of the thyroid gland; but this seems doubtful. It partly proves nothing about the nature of the complaint that it is possible to make the symptoms disappear by administration of thyroidin, and partly it would be somewhat artificial to imagine that the low basal

metabolism had an etiology in periodic catatonia different from that in the other types of schizophrenia.

Furthermore *Gornall et al.* in periodic catatonia have in the intervallary phase found normal amounts of protein bound iodine (PBI) in serum simultaneously with reduced basal metabolism. At the change into stupor the value of PBI remained unchanged, while the basal metabolism increased. This is in perfect agreement with the above-mentioned investigations by *Bowman* and *Reiss* and their collaborators with radioactive iodine in schizophrenics who were not periodically catatonic.

Finally it may be objected to the view of thyroid insufficiency in periodic catatonia that enormous doses must be used in the thyroxin treatment *ad modum Gjessing*, and that the treatment must be started at a definite point in the fluctuations of the phases, and that the metabolism is to be kept at about 110 per cent. in order to produce a proper effect.

According to the available information it seems most natural to assume that in schizophrenia there is generally a normal function of the thyroid gland, that the peripheral tissues react less than normally to it, or that there is an abnormal resistance to TH (or reduced sensitivity to TH) so that less oxygen of that offered to the tissues is used. In periodic catatonia there would then for some reason be a fluctuating resistance to TH.

Mansfeld in a number of interesting experiments has been able to show that the thyroid gland besides thyroxin produces other substances, which check the effect of the thyroxin. These substances, which he has termed thermothyryns, are supposed to appear in varying amounts dependent on external conditions. Thermothyryn A can be shown to occur in the blood, when the person in question has been exposed to intense action of heat, e.g. a hot bath. Thermothyryn B is found in the blood in summer independently of the external temperature. Serum from animals that had been cooled increased the metabolism. The thermothyryns, which check the effect of thyroxin, paradoxically enough bring about an increase in metabolism when injected into animals which have had the thyroid gland removed a couple of months previously. No details are available as to the way in which these thermothyryns influence the effect of thyroxin. These "*Mansfeld substances*" perhaps might explain the variations of metabolism in cases of catatonia and the above-mentioned discrepancy between the basal metabolism (consumption of oxygen) and the activity of the thyroid gland (determined by the absorption of iodine). It is uncertain whether these substances are identical with the antihormones mentioned by *Iversen*.

A disturbance of the enzymatic transformation of thyroxin into tri-iodothyronin might also be imagined as cause of the disturbances of metabolism in schizophrenia, if one follows the *Pitt-Rivers* theory of tri-iodothyronin as the TH proper.

Reiss (1952 b) maintains being able to increase the effect of TH and other hormones by administration of a vasodilatory substance, e.g. nicotinic acid or priscol (= benzyl-imidazoline); but my own preliminary investigations with vasodilatory substances have not given any sure results. For that matter the question of the function of the hormones is quite unclarified. It is presumably widely different for the various hormones and undoubtedly very complicated. It is hardly possible on the basis of the available information to evaluate the importance of the circulation for the effect of the hormones.

The antagonism between the thyroid gland and the adrenal cortex brought out by *Reiss & Hemphill* does not agree with the majority of the statements in the literature. In animal experiments injection of thyroxin gives rise to hypertrophy of the adrenal cortex. Patients suffering from Addison's disease as a rule have a low metabolism, and patients with hyperfunction of the adrenal cortex have an increased metabolism. Otherwise there are various conflicting statements (*Soffer*). In this connexion it should be noted that *Reiss* (1952 a) uses the absorption of radioactive iodine in the thyroid gland as a measure, but as mentioned above, this need not be identical with the TH activity in the tissues and the consumption of oxygen.

The enigmatic fluctuations in the nitrogen balance in periodic catatonia show that the nitrogen metabolism must occupy a central position in the pathogenesis of the schizophrenic disorders, or at any rate in the cases of periodic catatonia, as a prevention of retention of nitrogen makes all other symptoms disappear. *Gjessing* amongst other things imagines the possibility of an intoxication with some poisonous metabolic product which arises by decomposition of protein during the evacuation of nitrogen. There are various possibilities here, but this problem has not at all been investigated so far. As mentioned above, *Hoskins* has advanced another acceptable and interesting theory, that the psychical symptoms in schizophrenia are due to oxygen deficiency in the cerebral cells. This theory is in good agreement with the defective action of TH demonstrated, which is of importance for the cell metabolism.

N retention, vagotonia, and a low basal metabolism, which are found in the intervallary phase in periodic catatonia, are called the retention syndrome by *Gjessing*. Still, it seems natural to include in this the increasing water-binding capacity of the tissues and the decreasing

non-protein N in the blood, as these phenomena no doubt are directly interdependent. It is imaginable that a change set in as regards the water-binding capacity of the connective tissue, so that protein N, non-protein N, water, and salts were retained, perhaps something similar to what is seen in myxedema, so that the thyroid gland must here be considered an etiological factor. *Gjessing*, however, is of opinion that the checking of the diuresis at the stupor passage (the last day of "awareness" and the first day of stupor) is so pronounced (the diuresis at the hydration test may even drop to 100 ml) that at this time we are obliged to assume interference of the antidiuretic hormone of the posterior lobe of the pituitary. The spontaneous secretion of chlorine suddenly increases to double during the stupor passage, which puts one in mind of the adrenal cortex and its share in the regulation of water and the salt metabolism.

The psychical and other biological fluctuations in periodic catatonia are somehow connected with the bodily constitution. The more pyknic the type of body build is the more distinct and regular are the phases of the disorder. In some leptosomatic and asthenic patients, it is true, *Gjessing* could demonstrate psychical fluctuations accompanied by fluctuations in the nitrogen balance; but the fluctuations were irregular in duration and intensivity. The question then arises whether the nitrogen balance follows the constitution or the disease; but there is no material available to decide this question.

If, with *Gjessing*, we assume that the anomalies in the N metabolism demonstrated by him are the cause of the periodical catatonic psychosis, the question arises whether anomalies in the N metabolism are the cause of schizophrenic psychoses without catatonic symptoms or without periodicity. If this pathogenesis were considered to be more generally prevailing, stationary schizophrenic disorders showing vagotonia and low basal metabolism might be supposed to occur in patients whose condition for some reason or other had been stabilized at some point during the retention of nitrogen.

Comprehensive investigations with this approach to the problems are not available, but the fact that *Mall* obtained good effects of the thyroxin treatment *ad modum Gjessing* of schizophrenics who were not catatonic suggests a more universal importance of the nitrogen metabolism in the pathogenesis of schizophrenia.

SUMMARY AND CONCLUSION

In schizophrenia there seems to be dysregulation of the vegetative centres in the hypothalamus.

Investigations into the intermediary metabolism show that in active schizophrenic psychosis there are displacements between the intermediary metabolic products which suggest the existence of disturbances of the enzymatic processes at the transformation of the substances.

Investigations into the function of the adrenal cortex suggest that there is a disturbance in the enzymatic processes which give rise to the synthesis and decomposition of the AC hormones.

Investigations into the function of the thyroid gland in schizophrenia suggest that the normal amount of TH is produced, but that the tissues do not react normally to it, perhaps because of enzymatic disturbances or the occurrence of antihormonal substances.

Nitrogen seems somehow to occupy a central position in the pathogenesis of the schizophrenic disorders or at any rate some of them.

On the basis of the available information one gets an impression that *schizophrenia is a universal somatic disorder which appears as poor regulation of the intermediary metabolism, of the vegetative nervous system, of hormone production, and of the effect of the hormones in the tissues, which among other things gives rise to psychical symptoms.*

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SYMPOSIUM ON "SOME SOMATIC PROBLEMS IN SCHIZOPHRENIA"

By

IB MUNKVAD and MOGENS SCHOU

On February 5, 1955, a symposium on "Some Somatic Problems in Schizophrenia" was held at St. Hans Mental Hospital in Roskilde (Denmark). The symposium was arranged on the initiative of *Arild Faurbye*, under the sponsorship of the Research Committee of the Danish Psychiatric Association, and it was in several respects a new type of conference in Danish psychiatry. The number of participants was only twenty-four, and accordingly the symposium had the character of a round-table conference. No formal lectures were given, and under *Faurbye's* chairmanship the discussion was lively and quite informal. Another special feature of the conference was that, besides the psychiatrists, a number of specialists from other disciplines were present. They represented as varied fields as: Physiology, biochemistry, clinical chemistry, internal medicine, pharmacology, pathology, endocrinology, enzymology, and hematology. It was encouraging that so many non-psychiatrists could be induced to take part in a discussion of a field of research the problems and results of which is so little known to those working in general biology and medicine.

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Faurbye had prepared the soil by sending in advance to each participant a survey of some of the relevant publications in the field. This report, which served as a basis of the discussion, is published in this issue of *Acta Psychiat. Neurol. Scand.* and should be consulted. As will appear from *Faurbye's* paper, the symposium had one more special feature. No new clinical or experimental data were presented, and the discussion was primarily concerned with the possibilities and relative merits of the various approaches to the problem. The symposium was, and was intended to be, of an orienting character; it served to familiarize the representatives of the various disciplines with one another and with the terminology and special problems of this particular research field.

Considered as a whole the discussion centered around two main topics, and since, so far, they represent distinct approaches, it may be practical to deal with them separately even if they were not so treated during the symposium. Since the discussion was so informal, this review can only give an impression of the main ideas and viewpoints put forward, and no attempt will be made to mention each speaker or to record each contribution in detail.

A large part of the discussion centered around *Rolv Gjessing's* unique and well-known investigations on periodic catatonia. *Ström-gren* and *Lunn* both emphasized the diagnostic difficulties; some of the patients described by *Gjessing* might just as well have been diagnosed as somewhat atypical manic-depressives, and it seems dangerous to make any generalizations from *Gjessing's* findings in periodic catatonia to schizophrenia as a whole. Our knowledge of disease entities is

so limited that we had better confine ourselves to an investigation of correlations between bodily changes and single psychiatric symptoms or—if we are daring—psychiatric syndromes. And if we are interested in schizophrenia as such, a symptom like autism, which is almost pathognomonic to schizophrenia, might be a good choice. *Gjessing* agreed in these considerations and emphasized that he did not consider periodic catatonia in any way representative of “schizophrenia as such”. Periodic catatonia should only be regarded as a “model psychosis”, and it was actually quite incidental that his interest had been caught by this type of patients. Admittedly the group of hebephrenics might have been of equal, or even more, interest. It is a very unhappy thing that the original designation “the group of schizophrenias” has been replaced by the name “schizophrenia”, since this implies an etiological or pathogenetic entity which may be, and probably is, non-existing. It is also worth emphasizing that many psychoses appear to represent borderline cases between the manic-depressive psychosis and the so-called schizophrenia. Periodic catatonia may be visualized as standing somewhere between the two poles, some of the patients having a larger share from the manic-depressive side and some being more related to the hebephrenics. This being so, *we must investigate the single patient, with the utmost care and for a long period*. *Gjessing* stressed the extreme importance of eliminating the exogenous factors that may obscure the “pure” endogenous course and clinical picture of the disease; such factors as infections, variations in quality and quantity of the food, etc., must be considered important in this respect.

The question of controls was raised by *Jacobsen*; there was general agreement on the importance of these but also on the difficulty of obtaining proper control conditions. *Gjessing* had two normal persons living under exactly the same conditions as the patients for two months; neither of these showed variations like those observed in the patients. *Brochner-Mortensen* made the objection that only a partial control was obtained in this way since it is known that even in normal subjects muscular activity and inactivity may influence the nitrogen balance enormously, and it is impossible for the control subjects to imitate the muscle tension which is a prominent feature in the catatonic states. *Frøshaug* pointed out that in a study of a phasic disease like periodic catatonia the patients served, so to say, as their own controls. It was emphasized from several quarters that not only did investigations of this type present very great practical problems, but a meaningful interpretation of the co-variations observed was also extremely difficult owing to the complexity of the interplay between the central nervous system and the other organs. It might almost be

questioned whether this type of approach in itself can give any clue to the problem of the pathogenesis, let alone the etiology, of the disease or diseases called schizophrenia. This viewpoint was illustrated by a lengthy and, of course, futile discussion of the question whether the phasic nitrogen retention and other changes observed in the patients should be considered the cause or the effect of the catatonic phases or possibly parallel symptoms of a common underlying disturbance.

Some discussion was concerned with questions of pathogenesis and etiology. The theoretical possibility of a purely psychogenic origin of schizophrenia was only touched upon, but *Strömberg*, *Nørvig* and *Madson* emphasized the probable pathoplastic effect of psychogenic factors. The patient's psychological reaction to his disease may easily be a determining factor for not only a large part of the clinical picture but also for the course of the disease. *Schou* pointed out that these considerations may be of relevance in the evaluation of the effect of experiments with "hallucinogen-antimetabolites"; even if the "causing agent" were suddenly removed or neutralized, one might expect a certain "inertia" of the psychological mechanisms. *Kjerulf-Jensen* considered an enzymatic defect, probably in the central nervous system, the most likely common denominator for the complicated clinical and metabolic picture; one might even visualize a one-one gene-enzyme relation for this disease, as known from microbiological work and as exemplified in human pathology by sickle cell anemia and Faconi's syndrome. In this connection *Gjessing* mentioned Fölling's oligophrenia phenylpyruvica. *Strömberg* explained that genetic studies seem to indicate that the majority of the pathogenic factors in schizophrenia have a genetic background. The data seem to be compatible with a theory of a recessive gene-pair as the specific condition of most cases of schizophrenia, the penetrance being 50-60 per cent. The genetic defect may, through some metabolic intermediate link, give rise to only a brief and limited change of one of the basic mental functions, and all further symptoms may be of a purely "psychogenic" (and in principle psychologically comprehensible) nature.

There was a detailed discussion of the so-called nitrogen retention syndrome and especially of its abolition by treatment with thyroid hormone. *Gjessing* emphasized the importance of starting the treatment at the right time, viz. at the moment when the patient enters the phase of negative nitrogen balance. The main variations in blood and urine nonprotein nitrogen are due to changes in the content of urea, while the other nitrogen-containing compounds, amino acids, uric acid, creatinine, etc., show only very slight variations. The amount of nitrogen accumulated varied somewhat from patient to patient, but was

usually of the order of 15–30 grammes. *Gjessing* further emphasized that he did not consider the nitrogen retention in any way specific; it must only be regarded as a symptom of some underlying disturbance, and he found it natural to focus the interest on the thyroid or, possibly, the hypothalamus-pituitary-thyroid system. This idea was supported by *Asboe Hansen*; one of the functions of the thyrotrophic hormone is a fat mobilization by which fat is substituted by a mucine-like substance with a very high water-binding capacity, and a process of this type might explain the variations in water balance observed by *Gjessing*. He further proposed to use determination of fractionated lipides and protein-bound polysaccharides in serum as an indicator of the thyroid function. The question of a possible relation between thyroid function and nucleic acid metabolism was mentioned by *Gjessing*, who also pointed to the influence of the thyroid hormone on the cytochrome-C content of the organism. Recent evidence, as related by *Klenow*, supports a hypothesis of the thyroid hormone as an un-coupler of the oxidative phosphorylation. *Brochner-Mortensen* proposed to induce nitrogen retention experimentally by the use of testosterone, and *Kruhoffer* found that the role played by other hormones, e.g. the growth hormone, should also be considered. *Kjerulf-Jensen* observed that the phase duration of the changes in nitrogen balance (one to a few weeks, varying from patient to patient) might support the idea of the thyroid hormone being somehow involved, and *Jacobsen* advocated the use of tri-iodothyronine in the treatment of these patients. The gigantic doses of thyroxine necessary to influence the nitrogen balance of the patients—and tolerated by these—were commented upon by the internists, and the possible significance of this observation was discussed. *Gjessing* mentioned some possible reasons for the unresponsiveness of the patients to thyroxine: An inhibition of the thyrotrophic hormone; an inhibition of the thyroid hormone, possibly by some sort of anti-hormone; and a reduced iodination in the thyroid gland. These and other possible mechanisms were discussed, and the significance of considering other endocrine organs and also the electrolyte metabolism was stressed.

Schou outlined three different approaches which presented themselves in a study of the metabolic correlate of the major psychoses: One, exemplified by *Gjessing*'s work, is a study of the co-variations of the psychotic symptoms and a series of physiological and biochemical functions. This approach is technically extremely difficult, and the results are not easily interpreted, neither physiologically nor in relation to the psychotic process. Another line of attack is to study the mechanism of action of therapeutic measures that influence the psychosis. And

the third approach is represented by the drug-induced "model psychoses".

This led into the second main topic of the discussion. *Astrup* emphasized the importance of work of this type, and *Fakstorp* gave an extensive and up-to-date survey of the present standing of our knowledge concerning the so-called "hallucinogens". His contribution, which mainly treated the chemical aspects, dealt with the older compounds of this group, mescaline, cannabis, lysergic acid diethylamide, etc., and included also the now famous Saskatchewan report on adrenochrome and Woolley and Shaw's recent hypothesis that a serotonin (enteramine, 5-hydroxytryptamine) deficiency or antagonism is the cause of the schizophrenic psychosis.

The experimental and therapeutic possibilities of this approach were discussed at some length. *Strömberg* mentioned that amphetamine and pervitin, when administered for a long period of time, may give rise to schizophrenia-like psychoses, and *Schou* proposed, with every caution, to make an attempt at removing the hypothetical low-molecular toxic compounds from the body fluids and cells of a schizophrenic patient by dialysis of his blood in an artificial kidney. The basic differences between the clinical picture of schizophrenia and the effect of most "hallucinogens" was emphasized by *Jacobsen*, *Gjessing*, and others, and *Faurbye* warned against an identification of schizophrenia with drug-induced abnormal mental states. *Strömberg* emphasized the important differences between adrenochrome and the older "hallucinogens"; adrenochrome is derived from a compound occurring in the animal organism, whereas mescaline, LSD, etc., are all of vegetable origin; according to the literature "organic" symptoms are absent from the clinical picture, and, in contrast to the experiences with other drugs, adrenochrome intoxicated persons apparently fail to realize the experimental origin of their condition. All in all there was a feeling that a study of this group of compounds was both interesting and promising, even if a too optimistic attitude may not be warranted in view of the very few experimental and clinical data available so far.

Jacobsen concluded the symposium by thanking *Faurbye* for his initiative in arranging this conference. Both psychiatrists and non-psychiatrists had profited from the discussion, and the symposium may safely be said to have been successful as a new type of research conference.

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MENINGO-ENCEPHALITIS AND PSYCHICAL SEQUELAE

By

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That meningo-encephalitis is sometimes followed by more or less chronic psychical symptoms is well-known. Descriptions are available of sequelae after encephalitis lethargica as well as of those appearing after meningococcal meningitis (*Trolle* 1951, *Degen* 1945, *Pai* 1943, 1945, 1946, *Ballard & Miller* 1945), after poliomyelitis (*Skinhoj* 1949, *Luft & Müller* 1947), after mumps meningitis (*Oldfeldt* 1948); and after other types of meningo-encephalitis. The frequencies of such psychical symptoms found by these authors vary from 20 per cent to 60 per cent, according to the composition of their material. As a rule, these sequelae are described as a neurasthenic syndrome and may be regarded as analogous to the psychical disturbances after head injuries, carbon monoxide poisoning, and epidemic hepatitis (*Lagergren* 1952).

A problem of prognostic importance that has received relatively little attention is: What factors decide whether a patient will make a complete recovery or be troubled by later psychical sequelae? One might very well imagine the prospects of recovery to vary with the premorbid personality, with the site and severity of the lesions in the CNS as well as with environmental factors. In a review of 327 cases of meningococcal meningitis *Trolle* (1951) found the risk of psychical sequelae to be influenced by social factors, by the presence of any inherited predisposition to mental disorders, and by the severity of the meningitis. *Pai* (1943, 1945, 1946), who also studied sequelae after meningococcal meningitis, distinguished two syndromes: a neurotic and an organic one. According to him, the neurotic syndrome is prone to appear in persons with an inherited predisposition to, or an earlier history of, psychical instability; the organic syndrome, in patients who have no such predisposition, but who have had severe meningitis accompanied by delirium. However, *Pai's* material was fairly small and consisted of patients who had been referred to a hospital for mental

diseases because of sequelae and therefore neuroses were probably over-represented. In a similar material *Ballard & Miller* (1945) investigated the significance of the severity of the disease and of the premorbid neurotic predisposition and found at least the latter to be correlated with the severity of the sequelae. One of the purposes of the present investigations was to find out what factors may be regarded as favouring the development of sequelae after encephalitis.

Another point to receive attention was the frequency of states described by *Sjöbring* (1947) as "hypophrenic"; these are characterized above all by mental and physical languor, decreased tone, slightly impaired wakefulness, and often with secondary superimposed tenseness. Fatigue appears to be a common but by no means regular accompaniment of these symptoms. According to *Sjöbring*, the syndrome is due mainly to infections, especially chronic or repeated infections ("post-infectious asthenia") or allergic diseases, but also to other organic diseases or brain lesions. He ascribed the origin of the syndrome to lesions in the CNS, changes which he classed under the heading of "encephalitis", although the term "encephalosis" would probably have been more compatible with his theory. The second purpose of the investigations, then, was to assess the incidence of hypophrenia in a series of patients who had most probably suffered from "true encephalitis".

AUTHOR'S SERIES

The primary material consisted of all cases of acute encephalitis or meningitis seen at the Department of Medicine, University Hospital, Lund, during the 11-year period 1940-50. In order to avoid too many cases with pictures of gross organic disease and to secure a series of preferably viral origin, neither cases of infection with pus bacilli, tubercle bacilli, or syphilis nor cases of multiple sclerosis were included. Further, only cases satisfying the following requirements were accepted:

1. The onset must have been acute and the clinical picture must have more or less resembled that usually seen in acute encephalitis, i.e. it must have included such symptoms as headache, dizziness, neck-stiffness, malaise, vomiting, and fever. Thus, chronic cases in which more or less routine lumbar puncture had revealed an increased number of cells in the CSF were not accepted.

2. The number of cells in the CSF must have been increased. Only cases in which the initial puncture had shown at least 5 cells/mm³ were accepted (with the exception of 2 cases in which only the second

puncture had shown at least 5 cells, but in which the first puncture could hardly have influenced the results of the second).

No attempts were made to distinguish meningitis from encephalitis, firstly because it is difficult clinically to demonstrate inflammation of the brain substance proper and, secondly, because it is difficult to imagine meningitis without involvement of the underlying parenchyma.

The material selected according to these criteria consisted of 113 patients, who had in all probability had acute, non-bacterial meningo-encephalitis, referred to below simply as encephalitis. Of these, 4 (3.5 per cent) had died during the acute stage. This left 109 for the investigations. Information was obtained by means of questionnaires about all of the patients except one. Of these, 88 (80.7 per cent) co-operated and were reviewed by the writer.

Of the 88 reviewed, 54 were males and 34 females. The interval between the encephalitis and the review varied from 16 months to 12 years and 5 months. The age-distribution is given in Table 1.

TABLE 1

Age in years	At onset	At review
12-19	17	1
20-29	23	21
30-39	19	30
40-49	19	12
50-59	8	19
60-69	2	5
Total	88 patients	88 patients

The disease was thus commonest in the age classes below 50. (Patients below 12 years of age are admitted only to the Children's Hospital, Lund, and therefore are not included in this material).

In most cases the patients had been admitted to hospital soon after the onset of symptoms, usually within a few days, and practically always within 1 month. The acute onset was usually ushered in by headache, dizziness, malaise, and vomiting, and sometimes by neck-stiffness. Of the 88 reviewed, 86 had had at least one of these symptoms. The records contained notes of double vision in 14 cases, and of other subjective neurological symptoms in 11. Practically all of the cases had been isolated cases, no signs of an epidemic ever having been noticed during the years spanned by the material.

The objective findings made during the acute stage of the disease are given below.

	No. of cases
1. Neurological focal symptoms	48
2. Meningeal symptoms (neck-stiffness and/or positive Kernig's sign) ...	40
3. Papilledema (varying from diffuse papillary outlines to full-blown papillary stasis)	13
4. Psychical symptoms	23
5. General symptoms of infection	60

Thus, more than half had shown neurological focal symptoms, which, however, had often been only slight and diffuse, especially regarding nystagmus and reflex disturbances. The psychical symptoms noted during the acute stage were coma in 2, delirium in 6, somnolence in 8, and other psychical symptoms, sometimes probably linked to the personality rather than ascribable to the encephalitis in 9.

In the majority of cases the records contained no notes about the type of the encephalitis. In some cases, however, the encephalitis had appeared after a well-defined clinical disease and could therefore be classed. Thus, 2 cases could be classed as occurring in connection with rubeola, 1 with mumps, 2 with infectious mononucleosis, 1 with herpes zoster, 1 with rheumatic fever, 1 with rheumatoid arthritis, 1 with Loeffler's eosinophilia of the lung, and 7 with pneumonia. In some cases aparalytic poliomyelitis could be assumed. In the other cases the etiology was unknown. In no instance did the clinical picture suggest Economo's encephalitis. Of the two patients who had had rubeola encephalitis neither showed characteristic traits, except possibly mild sequelae (mainly memory disturbances), and then only by one of them. Of the patients who had had infectious mononucleosis, one had also had isolated transverse myelitis, an accompaniment apparently never before reported in this disease. In the post-rheumatic fever case, an exacerbation of polyarthritis had been followed by symptoms of gross injury to the brain stem with subsequent persistent sequelae. The patient with Loeffler's eosinophilia described elsewhere by *Alwall* (1943) had shown hemiplegia and a relative increase in the number of eosinophils in the CSF as well as other allergic manifestations, namely asthma, nasal polyps and polyarthritis.

THE REVIEW

Method.—Of the original material consisting of 109 cases, 88 were reviewed in 1952 by the writer. The review consisted of an interview, at which the personality pattern was investigated, a simple physical and neurological examination, and some simple mental tests. The most

important of these examinations was the interview, at which the subjects were questioned in accordance with a specially devised scheme. Inquiry was made into the family history, and a note was made of any disease before and after the encephalitis, social and economical status since birth, premorbid personality and present state of health. Body-build was assessed on purely clinical grounds by the method of Conrad using the dimensions pykno-, metro- and leptomorph and hyper-metro- and hypoplastic scales, the mental make-up being judged *ad modum Sjöbring*, and the psychological tests used were: 100-3 test, Bourdon's test, and repetition of a series of digits forwards and backwards.

Sjöbring has described 4 normal personality variables: capacity, validity, solidity, and stability, which are supposed to vary quantitatively and independently of one another. Division of a normal population into frequency groups according to the position of any of these variables on the scale will give a normal distribution curve. Most of the individuals fall within the large middle group and are called normo-variants, while those falling within the outer regions are called sub-variants and supervariants. Here it should be stressed that even extreme variants fall within the normal variation, even though they can predispose or favour the development of mental insufficiencies.

Capacity is the inborn property providing the possibility of intellectual development. The supercapable are thus the talented and the subcapable the less talented individuals, while the oligophrenics are as a rule not regarded as being normal but pathological variants.

Validity is defined by *Sjöbring* as the supply of energy available for psychical processes. The subvalid are cautious, pedantic, insecure, tense, readily tired, while the supervalid are self confident, enterprising, secure, and not readily excited. The subvalid, who correspond to Janet's psychasthenic type, are believed to be disposed to asthenic and obsessional reactions.

Solidity represents the degree of firmness in the psychical substratum. The subsolid lack this firmness and they have the power to dissociate single psychical complexes from the rest of the consciousness. Their behaviour is quick, flexible, impulsive, they have a vivid imagination but make up their minds quickly, they are subjective and are believed to be disposed to hysteric repression. The supersolid, on the other hand, are slow, reflective, circumspect, critical, and objective.

By stability *Sjöbring* means the power of habit formation (automatisation) of the psychical functions, whereby a high degree of automatisation also means a lower degree of emotional attachment. The substable have less power of such automatisation, everyday occur-

rences always have something new to them as if they had never experienced them before. They are therefore concrete-minded, hearty, interested in persons, and often seem heavy and clumsy: Thus the same traits as in Kretschmer's cyclothymic types or Bleuler's syntonie personalities. To the superstable on the other hand, experiences soon become habits and automatic and affectively indifferent, with the result that he reaches a higher stage of development with regard to abstract reasoning and psychomotor ability. The superstable are thus light, cool, elegant, clever, and theoretical.

Readers interested in a more detailed description of *Sjöbring's* theory are referred to *Essen-Möller* (1950), *Goldkuhl* (1943), *Kinberg* (1941) and *Wretmark* (1953).

SEQUELAE AFTER ENCEPHALITIS

Symptoms that completely abated within 3 months of the acute onset of the disease were said to be manifestations of convalescence and thus were not classed as sequelae. In 27 cases (30.7 per cent) the patients made a complete recovery, while in the remaining 61 (69.3 per cent) symptoms appeared in the later course. It was often difficult to decide with anything like certainty whether the encephalitis could be held responsible for the symptoms that appeared later. In the study of the causal relationship three classes were distinguished:

Causal relationship probable	36
Causal relationship possible	16
Causal relationship improbable ...	9
61 cases	

Classification according to the cause must, of course, be subjective and therefore uncertain. The symptoms were said to be due to encephalitis when they initially appeared in association with it and could not be explained in any other way. The reason why a causal relationship was found to be only possible in 16 cases, or improbable in 9 cases was:

Diseases other than encephalitis	10 cases
Constitutional psychical symptoms, often also with hereditary disposition	7 cases
Psychogenic factors	4 cases
Symptoms difficult to interpret, unreliable information	4 cases

Of the 36 cases in the first class, the sequelae were mild in 29, severe in 6, and in 1 the patient was periodically psychotic. In the other two classes the symptoms were mild.

There were thus 36 cases (40.9 per cent), in which the symptoms were probably sequelae after encephalitis, a figure which must be regarded as a minimum. If those cases be included in which the nature of the symptoms was uncertain, it will bring the number up to 52 (59.1 per cent), which must probably be regarded as a maximum figure.

In some of the 36 cases in the first class, the symptoms completely or partly abated. Thus, 9 of the patients had made a complete recovery, 8 of them within 3 years and the ninth within 6 years of the onset. As to the remaining 27, who still had symptoms at the time of the review, the sequelae had decreased in 15 and persisted unchanged in 12. In some of the cases in which the symptoms had abated, the regression had occurred within the first few years of the onset, after which they had persisted unchanged. Of the 12 patients in whom the symptoms had not regressed at all, 10 had had the symptoms for 6 years: in these, then, the prospects of a complete recovery are very poor. As to those cases in which the interval between the onset and the review was shorter, it is possible that some of the patients will improve or make a complete recovery.

SYMPTOMATOLOGY OF THE SEQUELAE

The commonest syndrome did not quite coincide with what is generally understood by the term neurasthenia, but rather resembled posttraumatic encephalopathy, in which it is not chronic fatigue that dominates the picture but increased fatigability and impaired tolerance to strain and stress such as noise, social intercourse with several people at a time (especially if there is much talking), new situations or alcohol. Especially impaired tolerance to spirits is typical and, as a matter of fact, one of the patients judged the rate of improvement by the amount of alcohol he could tolerate. On exposure to such strains headache, irritability, and vegetative symptoms appear.

The following symptoms were reported by the 36 patients with clinically probable sequelae:

Irritability	23 cases
Fatigue	22 "
Headache	20 "
Impaired memory	14 "

Difficulty in concentration	13 cases
Depression	12 "
Dizziness	10 "
Disturbed sleep	6 "
Aching pain	5 "
Disturbed balance	5 "
Unrest, anxiety	4 "

In isolated cases several other symptoms also appeared. Thus in one of the patients, a 29 year old woman, encephalitis was afterwards followed by a periodic psychosis with clouded consciousness, unrest and hallucinations, often in association with urinary retention. Another woman gave the impression of suffering from a slight schizophrenic defect at the review, and in this case one might well suppose the development of a schizophrenia-like psychosis after encephalitis.

In at least some 20 of the 36 cases the picture was dominated by an encephalopathic syndrome as described above. In some cases it was mainly an intellectual impairment with decreased sense of judgement, insight, thinking capacity, and memory. In a few isolated cases the picture was dominated by other psychological syndromes and in 10 neural symptoms were noted.

Only in 4 of the 36 cases did the patients show signs of the state described by *Sjöbring* as hypophrenia and in one of them the cause was probably not encephalitis but chronic bronchitis. In this case the hypophrenic picture was also striking, while in the others the hypophrenic traits were less conspicuous. Of the 52 cases without definite sequelae after encephalitis hypophrenic traits were seen in 4, but in 3 of them the picture was not pronounced and in the fourth the cause was probably pulmonary tuberculosis with exudation in the pneumothorax cavity. Traits of hypophrenia were thus seen in altogether 8 (9 per cent) of the 88 patients reviewed. In the evaluation of the frequency of hypophrenia, the sex and age distribution of the material must be taken into account, because hypophrenia is usually commoner among females than among males and more frequent in the lower age classes than in the higher ones. Of the 8 hypophrenics in the present material, 7 were females and represented 20.6 per cent of the 34 females examined. In a field study of a population near Lund, comprising 2550 persons, *Essen-Möller et al.* also studied the frequency of hypophrenia. Among the females, whose age distribution was roughly the same as that in the present material, they found hypophrenia with a total frequency of 22.1 per cent. However, one of the co-workers in that team found a higher frequency than the other three: the mean frequency found by these being 14.1 per cent. Though

the present material is too small to permit valid conclusions, the frequency of the hypophrenics appeared to be about the same, which suggests that hypophrenia is no commoner after encephalitis than in the population as a whole.

As mentioned above, the picture in the acute stage never resembled that of Economo's encephalitis and in no instance was full-blown Parkinsonism seen at the review. In 2 cases cogwheel rigidity of the arms and sometimes stiff mimicry and hypomobility were seen as isolated signs, but is is not sure whether Parkinsonism might not develop in some of them later.

Signs of mild nervous disturbances were demonstrated in 39 patients at the review, but they showed no correlation with the mental sequelae. Of 7 patients with more pronounced neurological signs, 5 had probable and 1 possible sequelae.

The following two case reports represent typical examples of mild sequelae after encephalitis.

Case 1. The patient was an undergraduate, aged 21. He had hitherto always felt well and inquiry into the family history revealed nothing of interest.

In September 1945, the patient was then 14, fever and headache developed, and the patient was admitted to hospital because of suspected sinusitis. Investigation failed to conform to the diagnosis of this condition, but neck-stiffness was observed and laboratory examination of the cerebrospinal fluid showed 118 cells/mm³, mainly polymorphonuclear. Neurological examination revealed no further evidence of a pathological condition. The fever and the increase in the number of cells gradually subsided in the course of a month, after which the patient was discharged. Apara-lytic poliomyelitis was suspected.

The patient took a 2 3 months' holiday before he returned to school. However, even then he felt tired, he was not so keen on studying as before, he found learning more difficult, especially mathematics, and he could not concentrate. He often had to read the same thing several times before he could grasp what he was reading, besides which reading gave him a slight headache. He found it difficult to converse with more than one person at a time. He often felt rushed and was readily irritated. Despite this he managed to pass his matriculation examination at normal age, though with difficulty.

At examination in 1952 decreased alertness, indecisiveness, and decreased wakefulness were observed as well as a slight depression.

Case 2. The patient was a station-master, aged 52, who had otherwise always felt well. His mother and maternal uncle had had nervous trouble.

In 1949, the patient was then 49, dizziness, double vision, headache, and vomiting developed. The temperature did not rise. He was admitted to hospital, where nystagmus was established and Romberg's sign was found to be positive. Neurological examination revealed nothing else of interest. Lumbar puncture showed 10.5 cells/mm³, mainly mononuclear. The acute symptoms soon disappeared, and the patient was discharged after 25 days in hospital.

However, on arrival home from hospital the patient did not feel well. For about one year he was troubled by dizziness, coordination difficulties, headache,

and irritability. In the beginning he was often so dizzy that he could not walk without a stick and even then not more than a short distance without becoming giddy. Especially when he had a headache he was very ill-tempered. He was readily irritated by any uncommon noise and if anyone spoke loud. He gave up the use of alcohol because his wife persuaded him that it only increased his irritability, although he himself did not notice any difference. Later he occasionally drank but had severe headache.

At review 3 years after the disease the patient had, generally speaking, recovered, although he sometimes had a headache and felt dizzy. No mental or neurological symptoms were demonstrable at the review.

Case 3. The following is an example of more serious sequelae after encephalitis with recurrent psychosis.

The patient was a female, factory worker, aged 29. The mother had had mild nervous trouble but inquiry into the familial history revealed nothing of interest.

The patient had not had menarche until 17 years of age and menstruation was afterwards irregular and with long intervals. Gynecological examination revealed genital hypoplasia, and hormonal therapy failed to produce the desired result. However, at 23 the patient became pregnant and delivery was normal. The patient had not otherwise had any psychical disease.

In November, 1940, the patient was then 17, headache, dizziness, nausea, and vomiting developed. Kernig's sign was positive (50°) and lumbar puncture showed a slight increase with 13 mononuclear and 6 polynuclear cells/mm³. The stretch reflexes were pronounced, but neurological examination revealed no further signs of interest. One month after the onset the patient was somnolent for a week, she had headache, she could not urinate at will and she could not eat by herself but had to be fed. She was, however, discharged symptom-free after 6 weeks in hospital.

Later the patient had spells of disorientation, motor unrest and hallucinations sometimes in association with urinary retention. On various occasions she was admitted to mental hospitals because of these spells. In the intermediate periods she sometimes had headache, dizziness, nausea and vomiting, and periods of fever of unknown cause, but on the whole she was able to manage her work.

Examination revealed hypophrenic traits: slackness, decreased wakefulness, poor power of concentration, and adiodochnesia but otherwise no mental or neurological signs of a pathological condition.

FACTORS FAVOURING THE DEVELOPMENT OF SEQUELAE

The reason why sequelae develop in some patients but not in others must be either the severity or nature of the disease *per se* or the nature of the patient or both.

1. The massiveness of the infection, its extent and localisation in the CNS might reasonably be of importance in the development of sequelae. Table 2 might be useful in forming an opinion of the severity of the disease in the present material at the time of first admission.

In those cases in which sequelae afterwards appeared, then, the average number of hospital days was higher than for the others, the

TABLE 2

	With sequelae (36 cases)	Without sequelae (27 cases)
Average number of hospital days	30.6	23.4
Number of cases with fever	24	20
Average duration of fever in days	8.6 (21 cases)	8.9 (20 cases)
Number of cases with involvement of the sensorium	7	2
Number of cases with neurological signs	13	9
Average number of cells/mm ³ in CSF ...	137	67

number of cells in the CSF was also higher, as was the number in which the sensorium was involved. This difference was not, however, statistically significant.

The material was also divided according to the severity of the acute disease into three equally large groups, A, B, and C, of which Group A represents the severely ill, C the slightly ill, and B the intermediate group. The distribution of the sequelae among these three groups is given in Table 3.

TABLE 3

Sequelae	A	B	C	Total
None	5	9	13	27
Probable	14	12	10	36
Possible	5	8	3	16
Improbable	5	1	3	9
Total	29	30	29	88

To judge from the table, the number of cases without any sequelae would decrease and the number with probable sequelae would increase with the greater severity of the acute disease. The difference was not, however, statistically significant.

2. In an investigation as to whether the occurrence of postencephalitic sequelae is dependent on the premorbid condition of the patients, the latter were classed according to:

- a. Sex
- b. Age
- c. Personality factors
- d. Hereditary factors
- e. Environmental factors

re a. Sequelae occurred in 24 (44.4 per cent) of the males and in 12 (35.3 per cent) of the females. This difference was not found to be statistically significant.

re b. It is apparent from Table 4 that the intermediate age classes show a relatively higher frequency of sequelae than the lower ones, both for men and for women (the higher age classes are too small to permit valid conclusions). The difference is not, however, statistically significant. Judging by an individual analysis of the females, the higher frequency in middle age does not appear to be related to the climacterium. No certain predilection of special reactive type was observed for any of the particular age groups, although females in the 40-50 age class often showed signs of emotional instability and tendency towards depression.

TABLE 4

Age at onset	Males			Females			Males — females		
	Number re-viewed	With sequelae		Number re-viewed	With sequelae		Number re-viewed	With sequelae	
		Number	Per cent		Number	Per cent		Number	Per cent
12-19 ...	9	3	33.3	8	1	12.5	17	4	23.5
20 29 ...	18	6	33.3	6	3	50.0	24	9	37.5
30 39 ...	12	7	58.3	6	1	16.7	18	8	44.4
40 49 ...	11	8	72.7	8	5	62.5	19	13	68.4
50 59 ...	3	0	0	5	2	40.0	8	2	25.0
60 69 ...	1	0	0	1	0	0	2	0	0
Total ...	54	24	44.4	34	12	35.3	88	36	40.9

re c. As to the mental make up, the patients were judged according to Sjöbring's personality radicals. The distribution is given in Fig. 1.

It is evident from the figure that supercapacity, subvalidity, and substability in the present material were seen more frequently among those in whom sequelae afterwards developed than among the others, while solidity was noted with roughly equal frequency in both groups. Of Conrad's types, the pykno- and leptomorph dimension corresponded well to Sjöbring's stability, while the hypo-hyperplastic scale showed no difference between patients with sequelae and those without. The difference between the expected distributions and the distributions found was analysed by the χ^2 test, but in no group was the difference found to be significant.

Percentage of reviewed cases with sequelae



Distribution of the material among Sjöbring's four variables and according to presence or absence of sequelae

Fig. 1.

re d. Here heredity is to be understood as the occurrence of mental diseases or other states of psychiatric interest in the parents, siblings or children of the patient. Of the 88 patients, 29 met this requirement, and the distribution is given in Table 5. As the occurrence of heredity was one of the reasons why the causal relationship between sequelae and encephalitis was considered uncertain, the groups in which causal relationship was possible or probable were pooled. The frequency of heredity in the groups with and without sequelae was the same as the overall frequency.

TABLE 5

Type of heredity	Probable and possible sequelae	Improbable or no sequelae	Total
Psychoses	4 (7.7 %)	3 (8.3 %)	7 (8.0 %)
Abnormal personality, alcoholism ...	5 (9.6 %)	1 (2.8 %)	6 (6.8 %)
Marked nervousness, suicide, etc.	10 (19.2 %)	10 (27.8 %)	20 (22.7 %)
Epilepsy	1 (1.9 %)	1 (2.8 %)	2 (2.3 %)
Total with psychological heredity	17 (32.7 %)	12 (33.3 %)	29 (33.0 %)
Total without psychological heredity	35 (67.3 %)	24 (66.7 %)	59 (67.0 %)
Totals for entire material	52 (100.0 %)	36 (100.0 %)	88 (100.0 %)

re c. Altogether 14 had been exposed to what is generally accepted as unfavourable environmental conditions. These environmental factors were partly such as had influenced the patient during childhood and adolescence (only child, adopted child, incompatibilities between parents, alcoholism, low socio-economic status) and partly such as had influenced the individual before, during or soon after the encephalitis (marital, erotic, economic, or social failure, occupational discontent, etc.). The distribution is given in Table 6.

TABLE 6

Unfavourable environmental factors	Probable or possible sequelae	Improbable or no sequelae	Total number of cases
Present	12 (23.1 %)	2 (5.6 %)	14 (15.9 %)
Absent	40 (76.9 %)	34 (94.4 %)	74 (84.1 %)
Total	52 (100.0 %)	36 (100.0 %)	88 (100.0 %)

Here, too, the groups with probable and possible sequelae were pooled because the latter group contained cases in which causal relationship was questioned just because of environmental factors. It was found that unfavourable factors can oftenest be demonstrated in cases with sequelae. The difference was not, however, statistically significant ($0.10 > P > 0.05$).

SUMMARY

Of the patients admitted to the Medical Department, Lund, during the 11-year period (1940-1950), a total of 113 cases met the requirements regarded as necessary for classification as acute aseptic encephalitis or meningitis. Of these, 88 were reviewed for the frequency of sequelae and factors favouring the development of such after-effects.

Symptoms that could probably be classed as sequelae after encephalitis were seen in 36 cases (40.9 per cent). Inclusion of the 16 cases in which the symptoms were possibly sequelae after encephalitis would bring the frequency up to 59.1 per cent. Thus, in the present material 40-60 per cent, or about half, of the patients had sequelae.

As a rule, the symptoms were of the same type as those seen after *commotio cerebri*. Hypophrenia (*Sjöbrink*) did not appear to be commoner than in the population in general. The investigation could not show that psychical heredity, premorbid personality, the severity of the disease in the acute stage, or unfavourable environmental factors had any influence on the development of sequelae.

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ENVIRONMENTAL DEMANDS AND RELIGIOUS NEEDS

By

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Our patients, whether neurotics, psychotics, or psychopaths, frequently use religious terminology to express their ideas and experiences. It is therefore remarkable that relatively little has been published from clinical quarters on the importance of personal dispositions and mental illness for religious beliefs and practices. What little has been written on the effect of these beliefs and practices on mental health, or the influence of faith on the course taken by mental illness, is frequently more expressive of the authors' personal outlook on life than it is based on any clinical observation and experience. Recently *Langfeldt* (1954) focused attention on certain forms of preaching and pointed out that these do not always meet the requirements of elementary mental hygiene. Two patients, who some time ago resided in the P. C. and whose case stories are reported below, may serve as a point of departure for a discussion of the importance of the environment for the religious beliefs and practices of the individual, as well as a discussion of the psychology and psychopathology of religious beliefs and practices.

The American psychologist *Knight Dunlap* (1946) considers religion "a normal product of man's conscious processes: his desires, his fears, and not least his planning for future contingencies."

Dunlap maintains that it is not possible to draw conclusions of any value for the psychology of normal religion from religious pathology. The psychological problems of religion, he says, are primarily problems of group psychology. The religious ritual is a product of the group. Without ritual no religion could develop, without ritual religion cannot be maintained, and according to *Dunlap* it is the rituals which create faith, not faith which creates the rituals. His point of view is that of the sociologist. One is tempted to ask: "How then do the rituals originate?" They are the product of the group, but must presumably have their roots in psychological and biological needs of the individuals.

These needs are unconscious and, as far as primitive rituals are concerned, relatively uncomplicated.

The truly primitive religiousness (religious beliefs and practices) is animistic. The individual projects his anxieties and expectations into the unknown which surrounds him. The woods, the mountains, the sky, and the subterranean world become populated by spirits and gods. A similar process can be observed in a delirious person. The patient projects his anxieties and gives a religious interpretation to his hallucinations and illusions. This interpretation, however, is influenced by his previous knowledge, and the religious experience is coloured by prevalent religious practices in his particular environment.

A few observations of moron psychotics will illustrate this point.

"30 year old lumberjack. The patient, with wife and three children, had been forced by circumstances to live with his parents. The wife and the mother-in-law did not get along well. There were daily scenes between the two, to both of whom the patient was emotionally strongly attached. In a fit of rage he beat his wife. Afterwards he dashed out of the house and went for a walk. Out in the fields he had a vision. He saw God in the sky, against the setting sun. A large figure with wings. The patient returned home. He was composed, but depressed and self-accusatory. The family was informed that he had been converted. He did not curse any more. He talked of God and Jesus in a naive way, and his behaviour was definitely changed. His religious interest was launched by this hallucinatory experience."

"39 year old farm hand. He had restricted himself to life in the home and had great difficulties in making personal contacts outside his home. All his life he had lived in sexual abstinence. He had to be intoxicated before he dared to go to the local dancing-hall on Saturday night. One night he was more or less seduced by a dairy maid. He got home but could not sleep as he was anxiously concerned with his experience. Later in the night he heard a voice, saying: "Come to me." He became very happy, got down on his knees and decided to break the "relationship" (which had lasted for about 30 minutes). From then on he was changed. He stopped drinking and did not go to the dancing-hall any more. He went out among people and preached that they must seek the help of God as His help is the most lasting. He gave testimony about "the water of life which quenches all thirst".

In both patients a change in motivation and a conversion was caused by a single hallucinatory experience while in a state of emotion. Part of the motivation for the conversion may be understandable, but it is difficult to explain why a lasting change (at least over some time) in the motivation and behaviour of the individual was caused by this single experience. In the cases just cited it is not merely a question of projected emotion. The experience was interpreted and elaborated by the patients. They did not talk of supernatural visions or voices, they talked of God and Jesus. The incident and the particular religion of their environment was integrated into a religious experience.

"Religiousness" is not a homonomic intellectual or emotional function. Nor is there such things as a specific religious sense. The American psychologist *Gordon Allport* (1951) talks of a religious sentiment.¹ One can perhaps talk of a religious attitude or a religious style of life. An attitude such as this gratifies various needs, and one assumes constitutional as well as environmental factors to be of importance in the development of this attitude. It is a relatively stable entity but not unchangeable. The religion of any individual always reflects his way of thinking and feeling as well as his characteristic behaviour pattern. It is distinctly an individual function. In the primitive personality it is an expression of uncomplicated needs, while in the mature personality it is a highly integrated function. *H. J. Schouw's* (1946) conception of "religiousness" as a primary, instinctive function must be modified. It was founded on observations of religious activities in the mentally ill. The vivid religious symptomatology in some mental illness was regarded as an expression of the instinctive basis of religiousness. This was considered a parallel to the greediness of feeding and the uninhibited sexual activity of certain groups of the mentally ill, expressive of marked regression. As a matter of fact the sexual need is an integrated need, too, a need in which the desire to copulate, the want to exhibit and to view (peep) are mere items. We do know that in abnormal psychic states partial needs are frequently exposed more clearly because the integration gives way. When religiousness is termed an attitude which subsumes a multitude of needs, the implication is that religiousness is understood as a highly integrated function. The fact that we, in the early stages of the psychosis (in which there is no marked regression at all) and in the milder states of psychic abnormalities frequently find expressions of religious ideas, wants and strivings, may be interpreted as the integration giving way and partial needs manifesting themselves, frequently in a dramatic form.

The psychological substratum of the religious sentiment is a rather complicated one, and one may ask how a sentiment with such a complicated structure can express itself in the relatively simple ways seen in various religious manifestations. Maybe the primitive religiousness and the partial religious tendencies are the more dominant while the more subtle religiousness does not necessarily express itself in specific religious terminology and activities. Indeed, we talk of a deeply reli-

¹ *Allport*: "A disposition, built up through experience, to respond favourably, and in certain habitual ways, to conceptual objects and principles that the individual regards as of ultimate importance in his own life, and as having to do with what he regards as permanent or central in the nature of things."

gious nature in persons who have never professed any confession, people who even express a straightforward critical attitude towards the religious manifestations of their environment. On the other hand the most dramatic religious activity, ecstasy, speaking with tongues, etc., may indicate that one is dealing with primitive and badly integrated personalities. Clinical experience seems to show that oligophrenics and certain types of psychopaths frequently are attracted by a milieu in which primitive and partial needs may be gratified. In "Totem und Tabu" *Freud* analyses the psychological roots of totemism. In the totemic animal which is sacrificed and devoured he sees a father substitute, and he believes that the roots of religion is the longing of the son for the father, and further, that the sense of guilt towards the father and the opposition against him are part of the religious development. The same ambivalence which is characteristic of the son's relationship to the father, is seen by *Freud* in the relationship of the primitive tribe to the totemic animal—and thus in the relationship of man to God. In "Zukunft einer Illusion" *Freud* maintains that the religious ideas are illusions, originated because man feels helpless and ridden by anxieties. The father is the protector of the child.

We are dealing with a depth psychological analysis of the roots of religiousness. The same line of reasoning has been followed by *Harald* and *Kristian Schjelderup* in their arresting study "Drei Haupttypen der religiösen Erlebnisformen" (1932). Besides a "Vaterreligion" they present a "Mutterreligion" and a "Selbstreligion", as three different and well-defined types of religious mechanisms in the dynamics of religiousness. In the "Vaterreligion" the believer is the child of God. God is the beloved, yet feared, and just father. The "Mutterreligion" is characterized by the longing of the individual for detachment from this finite world, a need for protection and the want for safety and a union with God. Finally "Selbstreligion" is more explicitly narcissistic, a striving for "Selbstvergöttlichung", an adoration of the divine in oneself. The religious need is expressed in the conceptions and activities of the individual, and the *Schjelderups* find a confirmation of their hypotheses in the kind of piety described by *Söderblom* and especially *Fr. Heiler*: The mystic tends to leave everyday living and the environment, and in ecstasy he experiences the deep and intense union with God. In the prophetic type *Heiler* says, there is no such denial of the normal way of life. On the contrary, this type demonstrates self-ascendancy. He is concerned with values and a striving for ideals. God is the lord, the king, the judge, the father. Whereas the mystic experiences the *union* with God, there is for him (the prophet) always a distance between God and the seeking man. In the mystic's

piety the analyst sees a regression to the state of rest in the mother. The ethics and concept of sin of the prophetic type, however, are tied up with the infantile sense of guilt towards the father.

It should be stressed that we are dealing with a depth psychological analysis of the religious motivation of man. The *Schjelderups* emphasize that one must always discriminate between the immediate religious life and the forms of religion we observe in society, the forming of which is conditioned by history and environment.

A study of religiousness should be interesting, from the point of view of social psychology, as mentioned in the introduction, as well as that of the psychology of the individual. Would not a study of the manifestations of the mentally ill give valuable information, too?

A good many of the religious conflicts of our patients are due to the fact that their experience-type ("Erlebnisform") is not in harmony with the form of religion predominant in the milieu in which they grew up or which they have later joined. A conflict between the needs of the individual and the demands of the environment is the result.

With these general remarks as a frame and reference the following case stories will be discussed:

Case no. 15338. Born 1920. Admitted to P. C. 8.23.1954. Inger was 9 years old when her father died. Of her father the only memory is that of seeing the body before the funeral. Her father's work (carpentering) was continued by the mother with hired hands. The mother was hard-working and managed to support herself and her 12 children. She took good care of the children, in particular the somewhat frail Inger whom she appears to have overprotected. Inger was afraid of the dark as a child. At school-age she was much troubled by headaches, which usually began when she was due to leave for school and passed by the time her siblings got home. Incidentally she was doing well in school. The family lived in a remote place and the children had few friends with whom to play, as the mother did not want them to go far away from the house. Just as Inger had finished elementary school she got pleurisy. Her mother did not want to send her to the district hospital and nursed her daughter at home. She stayed in bed for several weeks. After the illness the mother was even more preoccupied by Inger, and the mother's repeated admonitions to be careful got to be a bit pestering. Inger became naughty and insistent on her own ways. When, at the age of 18, she was offered a maid's position through a sister in the capital, she fairly fled the care of her mother. In the capital she had several siblings who now rivalled with each other in taking care of her, and she felt more "looked after" than ever before. A few months later she got an iritis and had to leave her position and live with some relatives.

Generally Inger behaved like most young girls. She was fond of dressing up, used some cosmetics, would accept a smoke and occasionally she went to a dance. She did not go steady with any boy.

At the age of 22 she attended a religious meeting with an elder sister. She was deeply moved by what she heard and realized that she needed God, she says. In the parental home there had been no interest in religion except in the sister mentioned above. Inger at once became a very active member when she joined the

sect (the Pentecostal Movement). Up till then she wore her hair short, but now she let it grow long as the congregation did not approve of women wearing their hair short.

She met her husband in the sect and married when she was 25. He works in a mechanical shop and is a somewhat infantile, weak, dependent, and easily influenced man. At the time of marriage he was an almost fanatic member of the sect. They have two children, 8 and 7 years of age.

The marriage looked like a good one. However, as Inger in a short period of time had two deliveries she felt it would be a good thing to have "a break". The spouse, however, maintained that if they were not to have any more children they had no right to matrimonial intercourse. On this proposal they had separate bedrooms and lived in sexual abstinence for several months. Inger was depressed by this development. She tells that she felt like the husband's housekeeper. Finally she decided that she would rather have children. She became pregnant again but aborted when she had an attack of a febrile illness. This took place three years before her admission to the clinic and except for the last six months the couple lived this period in abstinence, and there existed a marital disharmony. Inger was stubborn and hot-tempered. In the end, of her own initiative, she consulted a doctor and talked openly with him about her problem. The doctor interviewed the husband and proposed some sort of birth control. The married couple then resumed their sexual intercourse, but limited it to the so-called "safe" days of the menstrual cycle.

Inger was a good housewife. She endeavoured to make the very best of it for her husband and children. She rarely went visiting as she felt inferior and awkward in company. If the family had guests she was tense and irritable and displayed strong antipathies.

One day a deputation of female members of the congregation called on Inger. In the last few years Inger had withdrawn from the sect. She had suffered from frequent headaches and for this reason she had cut her hair short as it used to be prior to her entering the sect. This visit was then somewhat of a surprise for Inger. The ladies informed her that they found it rather unbecoming that she—a member of a dissenting sect—only had two children. When Inger told the husband of the visit he was very upset and for the first time he sided with his wife. He too withdrew from the life of this congregation, and instead he devoted more time to Inger and the children. Inger, however, became depressed and reproached herself for taking the husband away from the friends and the community of Christians. She talk very little. The husband recalled the advice of the doctor and tried to persuade Inger to take more adequate measures against conception, but she refused to do so with indignation.

The precipitating factor leading to hospitalization was a rather trifling conflict with a woman in the neighbourhood. Inger was first depressed, then more depressed than ever and revealed suicidal thoughts.

When admitted to the clinic she was conscious and oriented. She is rather small with a sallow grey colour of the skin and wearing large black spectacles and a dark dress, all of it lending an air of seriousness to her. Intellectually she appeared normal. She had a mild depression, but appeared markedly dysphoric, hurt, and with a tendency to project. At the same time she seemed to have considerable self-criticism. Her attitude towards the doctors was positive, and she acknowledged that she wanted help as she had become nervous "because of matri-

monial conflicts and religious troubles". She criticised her husband and siblings, who did not understand her and never would let her have her own way. She spoke with indignation of the pressure which she felt the members of the sect exerted on her. While she consequently refused any visit by her siblings, her feelings towards her husband were more ambivalent. In a way she had done him wrong, too, she said. She believed she had too strong drives. The night after the wedding the husband had found out that she was not virgo. This was due to a casual affair, a loose relationship, a single mistake. It happened before the marriage and she believed it to be forgiven when she became a convert. The husband did not seem to attach any importance to the matter, but she had a feeling that she had concealed something essential from him, that she had married on false pretences. This fact, she thought, had been a contributing factor to her compliant attitude towards the husband's insistence upon abstinence. She felt like a sinner who was not living up to his high standards. For this reason she did not at all like to think of herself as the one who had drawn him away from his religion. When he asked her to take steps against conception she felt his proposal as something debasing. She had not lived very satisfactory from a moral point of view, she had, however, always wanted to be a Christian, and had always been in sympathy with the sister who was the only Christian in the family, and who for this reason had suffered much. Gradually she realized that she needed God and God's grace. However, she had to be guided by God and not her fellow men, she said. When she cut her hair short again this was a liberation. It symbolized her liberation from the demands of other people. She did not believe that it was the demand of God that they lived in abstinence in matrimony. For this reason she had sought pastoral support, first in the congregation at home, and later in the near-by town. She did not, however, find any support for her point of view, and one of the elders told her that "she painted the devil on the bedroom wall". She then gave in and resigned from the life and activities of the congregation. She was now considering to enter the Church of Norway, even though this would be a humiliation in many respects. As for the children it would create even worse problems. She could not part with them and leave them to the sect and their Sunday school. But how to arrange matters if the children were to go with her? They were not baptized. Ought they then to be baptized now at the age of eight? Would it not constitute a serious trauma to them? They could not grasp the motivation for such steps and they would be put in a unique position among children of the same age.

Inger reasoned somewhat like this during her stay in the clinic.

A somatic examination showed no pathological findings, and EEG was normal. The Rorschach test showed an exceptionally high number of "white space responses", expressive of a generalized attitude of opposition (Cand. Psychol. Killingmo).

Inspecting the predisposing factors of Inger's case and her religious attitude a little closer we find the following: At an early age she lost her father. Her mother was domineering and overprotective. Already when a child she displayed neurotic traits, as anxiety and conversion symptoms. At a later stage she lacks self-confidence and compensates for this in a self-assertive, generally defiant attitude towards her environment. Her ability to adjust is limited. For a short while only she was self-supporting, and she had difficulties in establishing satisfac-

tory contact with the opposite sex. Before marriage she had a causal affair, with intercourse once. She was going out, she danced, dressed up and used cosmetics, however, she felt frustrated all the time. One day she went with her sister to a religious meeting and was deeply moved. She then devoted herself with great zeal to this new life. She joined an extreme sect and subjected herself to its exaggerated demands, thus she let her hair grow long. She married a weak, immature, and dependent man, generally accepting his wishes and points of view. She idealized her husband and respected his "high ethical standards". She betrayed a conscious feeling of guilt towards her husband because of her premarital conduct and acknowledged that she "for this reason might go to extremes to please her husband", that is, expiate her fault. The fact that she let her hair grow long may be interpreted as another expression of her need for atonement.

The religious experience is relevant to a need in Inger. However, the form of organized religion chosen by her is only relevant to some of her partial needs. In the long run it is not sufficient that her need of atonement and the demands of her milieu work in the same general direction. Idealization as a compensatory mechanism gives way. She sees no possibilities for identification. Her personal need runs into rejection and is countered with exaggerated demands.

Demand-sin-atonement. Even without being able to rely on a lege artis psychoanalysis one can find numerous indications of a "Vater-religion" experience-type in her reactions. Her experiences in childhood and adolescence do not indicate any disposition towards a "Mutterreligion". We are here pointing out only a certain superficial similarity, as we have no analysis on which to base it. There can hardly be any doubt that we are dealing with a character neurosis, and symptoms of her neurosis can be seen well in advance of Inger's introduction to the sect and her husband. As is always the case, her religious activities reflect the total personality, and the lack of harmony and gratification is obvious. Even though intellectually she was suited for depth therapy the clinic was not in a position to offer this service to her. Outside the clinic her social conditions were hardly favourable to long-term treatment of her case. In the first few interviews, however, a certain analytical orientation seemed to be indicated. Later on insight-therapy would be a more likely procedure. Inger realized that she was being accepted and in turn she learnt to accept herself and her dispositions. She saw that her milieu did not correspond to her personal needs, not even in the sphere of religious needs. We believe it to have been of considerable aid for Inger that this need in particular was being ac-

cepted, too. After the minister of the clinic had been contacting her, she found good support in him.

The husband's first reaction was a proposal to withdraw his membership from the sect. Later on he wanted to move out of this particular community, to flee the milieu. In the end he decided to stay. Inger accepted this decision, after the husband accepted the fact that she sought out a way somewhat different from his own. No doubt Inger was the more gifted and mature personality of the two. The tragedy was caused by her submittal to his demands and her acceptance of his form of religion.

Incidentally the case clearly demonstrates how psychotherapeutic treatment may be a prerequisite of pastoral aid *sensu strictiori*. On the other hand the contribution of the minister was of great importance in this case in which the treatment from a certain stage and on, had to be accepting, covering up, and guiding.

Case no. 15435, born 1916. Admitted P. C. 10.4.54. Berte comes from a modest home in a small town community. Her upbringing was very strict, including considerable spanking. Her parents had no religious interests. As a child Berte was shy, but did not otherwise betray any nervous traits. When she had finished elementary school, without being remarkable in any respects, she passed a commercial school and then got a job as a saleswoman in a store. She kept this job until she married. She met her husband at the age of 19, and they went steady for seven years before marriage. In this period they enjoyed going for walks, would go to coffee-shops and occasionally to the movies. Berte thinks they had a wonderful time. She got away from the strict atmosphere of her parental home. Her fiancé, however, had to bring her home no later than 10 o'clock, in order not to provoke anger, in particular that of the mother. Except for a childish fear of "trouble at home" the fiancé did not notice any signs of nervousness in Berte. When the engagement had lasted for five years the fiancé one day informed her that he had been converted and wanted to become a Baptist. He had a brother who was a Baptist, but had never shown any interest in religious matters himself. Berte was thunder-struck. This was the end of their happiness. The small joys they had shared would be sins now, she thought. She became irritable and would flare up on small provocations. The engagement was broken off. When they met in order to divide various things which they had gathered for their future home, Berte broke glass and porcelain. This seemed somehow to constitute "abreaction". A reconciliation came about and they tried to continue the engagement. When finally they married in 1942 she was filled with anxiety, scepticism, and some defiance. He talked her into attending meetings and gradually she was moved by what she heard and arrived at the conclusion that the Baptists' point of view, e.g. on baptizing, was just the right one.

About this period her symptoms appeared as anxieties, dizziness, and oppression in the chest. She was afraid of crowds, and at the meetings she had to be seated in the very rear on the end of the bench. Already at this early point in her illness she noticed that her anxiety only presented itself at the meetings. By and by she stopped attending them. Her husband, however, continued as before. He had been "fully baptized" and held a number of offices in the congregation. Now and then

they had quarrels over these affairs. Berte accepted his faith, but she "did not like this business about tongues, interpretation, and the "full baptizing." Her anxiety-attack continued at home and in the end her husband stayed at home in order to look after her. In a way he realised the meaning of her attacks and he cut down on his activities in the sect and ended up as a fairly passive member of the sect. Berte's attacks, however, took such proportions that her doctor recommended hospitalization.

She was a florid pycnic. When admitted to the clinic she was conscious and oriented. Intellectually she was a little below the average. She had a mild depression and was noticeably inhibited, but natural and with adequate contact. She complained of anxiety, oppression in the chest, etc., and she mentioned that she had some matrimonial and religious problems, but she did not connect these with her attacks. Her husband appeared to be intellectually superior to her. He was calm and composed and had given considerable thought to his wife's illness. He could not understand, he maintained, that the wife really had religious problems, as no pressure had ever been exerted on her, and she had joined him of her own accord. He did believe, however, that she was jealous and that she simply could not stand that he had any interests besides her. Gradually he had come to pay due respects to her tantrums. As long as he stayed at home with her she would be humble and good and lovable. Occasionally he wondered if she might be troubled by a feeling of guilt as she would sit down on his lap and ask him to hit her. She would then be sorry and remorseful that she had criticised his faith in such mean terms.

Berte admitted that whatever her husband said was all very well, but he impressed her as being "so annoyingly indulgent" towards her that she simply had to ask him to hit her. Their sexual relationship was, they both agreed, good. They had no children.

After the husband's visit, confrontation with all the information and talks between the couple and the doctor, Berte began to show signs of homesickness. She minimized her former complaints and accusations and maintained with some force that certainly her husband was entitled to have his interests. There were, she comforted herself, "a good many men who had much more dangerous interests". From now on everything would be nothing but happiness.

This case is fairly different from the previous one, regarding the predispositions of the patient as well as the dynamics of the symptoms. To start with one was under an impression that the patient had seriously tried to understand her husband but that she could not accept and identify herself with the sectarian milieu, and thus a conflict had arisen for her. Later one was more inclined to think that she really had tried to accept the milieu, but hardly as an expression of a genuine religious quest. It was rather a manifestation of her want for a deeper contact with people, in particular a need to be closer to her husband and to identify herself with his interests.

The treatment demonstrated to her her tendency to be jealous. The visit of her husband and the frank talk between them increased her insight into the situation. It is perhaps a little conspicuous that she

reacted so strongly to the tongue speaking, being a pronounced hysteric. At any rate the intense activities of the sect and the fact that her husband was so strongly engaged in it had a provoking effect on her.

In this case one dares not attempt an evaluation of the patient's personality in relation to the three "experience-types" (*Erlebnisform*) previously described. The "Vaterreligion" with its pattern of demand-sin-atonement might in Berte have called up memories of the parental home. "Mutterreligion" might offer her the warmth and love she is longing for. She was perhaps most inclined towards the more narcissistic "Selbstreligion"? She was not suited for analytical treatment and we do not know the answer. We were dealing with an immature and insufficiently integrated personality. Even though her husband suggested a talk with the clinic minister, she did not want to see him at all. In her neurosis a religious conflict was not the essential problem.

The fact that the religious behaviour of an individual always reflects the total personality and the fact that his image of God always reflects his needs,—these facts do not in any way prove or disprove the validity of the religious notions. Faith is based on certain personal assumptions, just as infidelity is, too. When, however, the object of faith or the preaching does not correspond to the needs and assumptions of the individual, a conflict evolves, a conflict which probably often creates a neurosis.

SUMMARY

The case histories of two patients serve as pointers for a discussion of the importance of the environment for the religious beliefs and practices of the individual, as well as a discussion of the psychology and psychopathology of religious beliefs and practices.

The religious sentiment has rather a complicated substratum. Subtle religious beliefs does not necessarily express themselves in a specific religious terminology. On the other hand the most dramatic religious activities, such as ecstasy, speaking with tongues, etc., indicate that one is dealing with primitive and badly integrated personalities.

A study of the manifestations of the mentally ill may give valuable information about the psychological substratum of religious beliefs and activity. Many of the religious conflicts of our patients are due to the fact that their religious "experience type" is not in harmony with the form of religion predominant in the milieu where they grew up or in which they now live.

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ON THE EFFECT OF SUAVITIL (BENZILIC ACID
DIETHYLAMINOETHYLESTER HYDROCHLORIDE)
ON THE HIGHER MENTAL FUNCTIONS OF NORMAL
SUBJECTS

By

HELLE KEHLET MUNRO

It has been shown that benzilic acid diethylaminoethylester, hydrochloride, $(C_6H_5)_2COH.COO.CH_2.CH_2.N(C_2H_5)_2$, HCl, (*Suavitil* (R)) in small doses has a pronounced effect on some higher functions of the central nervous system.

The compound has an anticholinergic effect measured on the isolated guinea pig's intestine corresponding to about 1/3 of that of atropine. Its effect on the central nervous system is, however, more pronounced. After 5–7 mg given to humans it gives subjectively a feeling of dizziness, heaviness in the limbs, and a slight thought block; and objectively a disappearance of the α -waves in the EEG. In animals under normal circumstances it gives only few symptoms, but when they are submitted to a slight mental stress, the behaviour of the animals (rats and cats) is normalized (*Jacobsen* and *Sonne*, 1955; *Jacobsen* and *Skaarup*, 1955). In man, smaller doses than those giving subjective and objective symptoms diminish the autonomic responses to emotion (*Jacobsen et al.* 1955). Clinically, this drug has been used with some success in psycho-neurotic states (*Munkvad*, 1955).

Its main effect in small doses seems to be to increase the emotional threshold for outer influences, an effect which is seen in the experiments mentioned with animals and humans. It is, however, important for the clinical use to know to which extent the intellectual functions are impaired after administration of Suavitil in moderate doses. The experiments reported in this paper give an orientating analysis of this effect of the drug.

TECHNIQUE

Experimental subjects: The experiments were made on young healthy adults of above average intelligence and education, and assumed to be without mental anomalies, (the usual easily accessible group of volunteering students, being payed a small sum to reduce sampling error). The total group consisted of 5 females and 7 males, of which the first 4 were used in pilot experiments and omitted from the final analysis of the results.

Administration of the drug: Suavitil was injected subcutaneously in doses of 4 mg dissolved in 1 ml saline. This dose is somewhat higher than that clinically used (1–2 mg perorally) and shows a subjective effect on most individuals. On the other hand, 5–7 mg are necessary to provoke marked symptoms, including the blocking of the α -waves. The marked symptoms usually appear about 5 minutes after the administration and disappear after some 45 minutes. The time of the testing was limited to the first hour after the administration. In the control experiments, 1 ml saline was injected subcutaneously.

The tests: Each test was prepared in 2 parallel forms (sets A and B) and cross control was used to eliminate a possible difference between the forms and any retest effect. Four of the subjects were tested with Suavitil injections first; the other four with saline first, and in each group two subjects were tested with set A first, and two with set B first. The tests were always given in the order indicated below.

The following tests were used:

(i) *Memory test* (presented 1–3 minutes after the injection, recalled 25–30 minutes after the injection). A logical (meaningfull) passage was read to the subject shortly after the injection, *i.e.* before the effect of the drug had set in. The recall was tested after the administration of the 3rd test, the subject being asked to write down as much as he remembered from the passage. As a score the number of ideas recalled was used. The selections were taken from the Danish Binet (set A) and from Wechsler's Memory Scale Form I (set B) the division of ideas being the same as for the standard administration of these.

(ii) *Serial sevens* (begun 8–11 minutes after the injection): The subject was asked to count backwards by sevens starting from 103 (set A) or 104 (set B). The number of errors was used as a score.

(iii) *Jigsaw puzzles* (begun 10–14 minutes after the injection): For each set there were used 8 coloured postcards showing well-known places in Copenhagen. The cards were cut in 6, 9, or 12 equal, rectan-

gular pieces. Each picture was presented separately, and the subject was asked to put it together as quickly as possible. He was not told what it would represent. After each puzzle, he was asked to assess the time he had spent on it. At the end of the session, about 20–30 minutes later, he was asked which pictures he had done. This test thus became (a) an intelligence test of visual-motor speed type; (b) a test of judgment of filled time (i.e. time spent on a task); and (c) a test of recollection of situations not specifically presented for learning. The sum of seconds spent on each puzzle was taken as the score for (iii) (a); the sum of differences between estimated and real time in seconds for (iii) (b); the number of puzzles recalled for (iii) (c).

(iv) *Digit-Symbol* (begun 27–39 minutes after the injection). A modification of Wechsler's Digit-Symbol test was used. Set A and B consisted of the odd and even numbers from Wechsler's Intelligence Scale Form I, respectively. The subject was asked to mark with a vertical pencil stroke whenever the examiner tapped her pencil. This was done every 10 seconds. The test was continued for 4 minutes. In this adaption the test became less an intelligence test and more a visual-motor speed test with distraction added. The number of characters drawn within the time was used as score.

(v) *Verbal fluency* (begun 32–44 minutes after the injection). The subject was asked to write on a sheet of paper as many words as he could think of beginning with a particular letter, T for set A and R for set B, (two initial letters occurring with about the same frequency in the Danish language); and to mark with a vertical stroke the last written word whenever the examiner tapped her pencil (every 10th second). The time limit was 4 minutes. The number of words written was used as score.

(vi) *Abstraction test* (begun 37–49 minutes after the injection). The subjects were asked to find the principle of order in 7 written letters and add an 8th that completed the series, and again to mark tappings repeated at 10 second intervals. There was no time limit. Part E of the United States Employment Services General Aptitude Test Battery including the samples (except No. 11) was used; the odd numbers for set A, and the even numbers for set B. This test was included as a fairly pure intelligence test, the aim also being to assess the relation between the level and speed of intellectual functioning.

(vii) *Rating Scale*. As a supplement to spontaneous remarks and casual questioning about subjective effects of the injection, the subjects were asked to check with 0, (+), +, or ++ a list of 33 symptoms such as sweating, headache, tension, etc., some symptoms which could and others which could not be expected. The list was the same

in both sessions: Each (+) was given 1 point, + was given 2 points, and ++ 3 points.

(viii) Finally the subjects were asked to estimate the total duration of the whole session.

RESULTS

The results of the experiments can be seen in Table 1. For all tests the scatter is fairly large in spite of the homogeneity of the sample. In view of the shortness of the tests, reliability is probably low for all of them. Besides, it appears that set A and B have been of different levels of difficulty for tests (i) and (v). However, as there is no difference between the means for the experimental and control data on these two tests, a reduction of the scatter by correction for the level of difficulty would probably not bring out significant results, and is therefore not attempted.

A more detailed analysis indicated that on test (iv) the speed remained fairly constant over the 4 minute period both in the experimental and the control session, hence the difference between the total number of symbols drawn gives a clear measure of the effect of the drug. For tests (iii), (v), and (vi) the items varied in difficulty and the working speed was uneven, no pattern appearing in these experiments. Therefore a measure which would fully define the effect of the drug was difficult to devise, and the figures used here are only crude indexes.

The symptoms described by the subjects in test (vii) show a different distribution over the various items in the control and the experimental groups. Those in the control experiments were more like ordinary examination anxiety symptoms. However, there was a considerable overlap, and the suggestibility of the subjects was surprising (Table 2). There appeared to be some correlation between the number and type of symptoms felt in the control experiments and those felt in the experiments after administration of Suavitil. Two of the subjects were strongly influenced by the drug: one (No. 3) nearly collapsed, and the other (No. 5) laughed uncontrollably. Both stated also some symptoms after the injection of saline. One subject (No. 7) appeared moderately affected. The remaining 5 had only mild effects and 2 of these (Nos. 2 and 6) also showed symptoms in the control experiments. The most common symptoms registered after administration of Suavitil were a general feeling of not being fit, dizziness, paraesthesia in the limbs, metallic taste, drowsiness, dryness in the mouth, accommodation difficulties, and a feeling of heaviness of the limbs. Most

TABLE 1
Result of the Test.

Experimental subject No.		1	2	3	4	5	6	7	8	Remarks
Sex		M	F	F	M	M	M	M	M	
First experiment ¹⁾		C.A	E.B	C.B	E.A	C.B	E.A	C.A	E.B	
i Memory test	E	16	15	8	8	15	10	13	9	
Number of ideas recalled	C	9	10	10	12	14	12	13	12	
ii Serial seven	E	0	1	0	1	0	2	2	1	
Numbers of errors	C	0	4	0	0	1	1	1	0	
iii Puzzles a) duration	E	562	498	596	629	428	726	227	399	
in sec.	C	537	409	438	341	567	423	283	220	
	E-C	25	91	158	288	-139	303	-56	179	
b) estimated duration	E	-72	27	964	61	522	894	678	201	2
Time duration in sec.	C	-127	-114	107	-106	438	87	32	-132	
	E-C	55	141	857	167	84	807	646	333	
c) numbers recalled	E	6	8	4	7	5	5	5	5	3
	C	7	8	6	8	6	7	8	6	
	E-C	-1	0	-2	-1	-1	-2	-3	-1	
iv Digit symbols	E	197	179	88	185	161	130	150	198	
numbers done	C	203	217	143	175	195	112	229	250	
	E-C	-6	-38	-55	10	-34	18	-79	-52	
v Verbal fluency	E	46	39	11	40	41	24	36	24	
numbers done	C	33	51	27	33	36	17	43	32	
vi Abstraction test	E	0	2	9	5	2	2	3	2	
a) Numbers of errors	C	1	2	9	4	0	4	3	2	
b) Time in sec.	E	310	315	240	166	400	255	360	310	
	C	360	207	285	240	540	375	290	215	
vii Rating Scale	E	3	7	16	10	8	20	10	10	2
Score (3, 2, 1, 0) on each symptom noted	C	2	8	10	0	9	10	4	0	
	E C	1	1	6	10	1	10	6	10	
viii Estimated duration	E	-5	0	-18	0	-15	-15	0	12	2
of total experiment	C	-	-20	0	0	0	-35	15	-15	
— real duration, time in minutes										

¹ E = experiment

C = control

A = set A } For subjects 2 and 8, however, form A and for 4 and 6

B = set B } form B of test *iii* was given in the first experiment.

² Significant at 5 % level } On Mann & Whitney's U-test

³ Significant at 1 % level } (Annals of Mathematical Statistics, 1947).

TABLE 2

*Frequency of common symptoms (irrespective of degree) in control and experiment.
This table is based on 12 subjects (pilot sample included).*

	E	C
Feeling of weakness in muscles	9	5
Difficulties of fixation	8	5
Dizziness	7	2
Dry throat	7	3
Muscle tremor	7	7
Feeling warm	6	7
Difficulties of concentration	6	5
General feeling of unfitness	5	0
Paraesthesia in extremities	5	1
Difficulties of accomodation	4	2
Feeling cold	4	3
Sweating	3	5
Euphoria	3	4
Taste of metal	3	1
Headache	2	3
Sounds are perceived distant	2	2
Unreality feelings	2	1

of these symptoms have occasionally been observed as side effects during the clinical use of the drug. Three of the subjects stated the effect to be a pleasant one similar to slight alcoholic intoxication.

The symptoms were not always apparent at the time of test (ii), reached their maximum during the tests (iii) to (iv), and in one or two cases they had cleared up at the time of test (vi). It is possible that some of the tests made at the beginning and towards the end of the experiments would show significant differences if they were made while the symptoms were at their peak.

DISCUSSION

The number of experimental subjects is rather limited in proportion to the scatter of the results. It is possible that statistically significant differences between the control- and the experimental testing could be found on more tests if the number of subjects was increased. However, some conclusions can be drawn from the experiments.

No apparent change after the administration of Suavitil was found in the level of intellectual functions measured as the ability to subtract (test (ii)), to do puzzles (iii), to associate (v), and to make abstractions (vi). Nor were alterations in the speed of functioning under di-

straction found (tests (iii) (a), (iv), (v), and (vi) (b)) in spite of the fact that the subjects complained of poor concentration. As regards memory functioning, the results were at variance. No difference could be seen in the recall of a logical passage (test (i)), but this was presented before the effect of the injection had begun, although recalled in a period when the symptoms were rather pronounced. The memory for situations not specifically presented for learning was clearly affected (test (iii) (c)). Probably this is a higher organized function (more abstract in Goldstein's sense) and more related to functioning in life situations than is the recall of a passage presented for learning.

The assessment of time ((iii) (b) and (viii)) was impaired. This may reflect a change in the sense of time, or it can be an expression of the fact that the subjects felt it more difficult to carry through the tests with Suavital than without. In the first 4 experiments the subjects were asked to assess empty time (to indicate when they thought that 10 or 15 seconds had passed from a given signal). With this technique no difference was seen between the two experiments. The judgment of filled time is probably a very abstract process.

As mentioned, the doses of Suavital given were somewhat higher than the single doses used therapeutically. The present experiments suggest that even after a 4 mg injection only a slight effect, if any, is seen in ordinary intellectual efficiency. On the other hand some highly organized functions related to the registration of a situation simultaneous with attention to a task seem impaired, although not to any great extent.

SUMMARY

With a battery of mental tests a limited investigation was made into the effect of Suavital (benzilic acid diethylaminoethylester HCl) on the higher mental functions of 8 young healthy adults of both sexes. The given doses of 4 mg were higher than those generally used clinically. No effect could be seen on the ordinary intelligence functions, but some highly organized functions, related to registration of a situation simultaneously with the attention to a task appeared somewhat impaired.

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TREATMENT OF PSYCHOSES AND PSYCHONEUROSES WITH A NEW SEDATIVE (SUAVITIL)

By

IB MUNKVAD

Suavitil is benzilic acid diethylaminoethylester hydrochloride. It represents a type of compound with an effect on the central nervous system different from the types of sedatives hitherto used in therapy. Experiments with animals and human subjects have shown that, apart from its anticholinergic effect, it seems to raise the threshold for psychic irritation (*Jacobsen & Skaarup*, 1955 a, 1955 b; *Jacobsen & Sonne*, 1955; *Jacobsen et al.*, 1955 a, 1955 b). As soon as this effect was discovered it was decided to submit this compound to therapeutical trial, and the result of this trial is reported here.

EXPERIMENT ON TREATMENT OF PSYCHOSES

22 psychotic patients have been treated¹:

Schizophrenics (chronic, catatonic forms)	9
Schizophrenics (chronic, paranoid forms)	4
Schizophrenics (fresh, paranoid type)	1
Huntington's chorea, Dementia, Schizophrenia	1
Endogenous depression	4
Endogenous mania	1
Paranoid climateric psychosis	1
Depressive state in mental inferiority	1

The patients were observed for a sufficient time to allow evaluation of their clinical state. Thereafter Suavitil or placebo were generally ad-

¹ We are indebted to senior physician Otto Jacobsen, M.D., "Sindssygehospitalet Nykøbing, Sjælland" for the permission to carry out experiments on the chronic schizophrenic patients.

ministered for 1 week each. For the first few days the dose was 5 mg 6 times daily, later 10 mg 6 times daily, to a few cases as much as 15 mg 6 times daily perorally or subcutaneously. No systemic toxic effect was seen during this treatment.

Three of the schizophrenic patients possibly appeared less tense and stereotypic, and rhythmic movements disappeared for a period, but in general no improvement was seen. Five patients in these groups were lobotomized a few weeks later, and in two of them a slight effect of the operation was observed. These two patients, however, were not found to be influenced by the medication.

In the patient with fresh schizophrenic symptoms an obvious effect was seen after administration of Suavitil, with a relapse after discontinuation of the treatment; the possibility of a spontaneous remission in this patient cannot be excluded; the patient was transferred to another hospital for other reasons, and Suavitil had no effect on this patient some months later. In the depressive state there was no effect at all. In the maniac patient a certain sedative effect was seen, but as it was the very first patient under this treatment, it was held safer to continue the necessary treatment with electric shock. The rest of the patients with psychosis showed no improvement.

EXPERIMENTS WITH PSYCHONEUROSES

In the experiments with the psychoneurotic patients, it soon became evident that it was impossible to obtain conclusive results as long as the patients of this type remained in the hospital. Here an improvement is seen in most cases, simply due to the mere effect of the hospital atmosphere. Moreover, it was found difficult to withhold other therapeutic measures, such as direct or indirect psychotherapy from the patients. For this reason it was decided to make the experiments on ambulatory patients in their own surroundings. Only patients whose disease seemed to be stationary, and who previously had been treated for some time without or with little result, were considered suitable for the experiment. The earlier treatment had been insulin-therapy or ECT, in other cases intensive psychotherapy, sometimes in the form of psychoanalysis. This series has been supplemented with a few other patients who had been under group-therapy with some improvement in their condition, mainly because they were examined more closely for their autonomic reactions.

During the experiments the patients were not submitted to any other kind of treatment. Reassurance was avoided as much as possible. No other medicaments were given, except that the patients were al-

lowed to take barbiturates for insomnia if they were accustomed to do so. They visited the investigator once a week and received tablets for the coming week. Their spontaneous remarks about their state were noted, and thereafter some standardized questions were asked, as far as possible without any indirect psychotherapy—the interview only lasted about ten minutes. Only peroral treatment was given. In most of the experiments, placebo tablets of the same size, form and taste were given during the first 2–5 weeks of the experiment, after which the true tablets were administrated. This form of treatment was choosed in order to prevent the patients to discover frequent interchanges of the tablets during the long periods of investigation. In one experiment placebo tablets were given for periods, alternating with the test tablets. The investigator knew about the alternation between placebo and he true tablets.

The duration of treatment varied from 10 days to 1 year. At the beginning of the treatment Suavitil was given in dosis of 0.5 mg 3 times daily, which doses were increased slowly up to 1.5 mg 3 times daily. No sideeffects of importance were observed.

The diagnoses, the patients' main symptoms, the duration of the treatment, the dosage and the results of the treatment are given in Table 1.

A more detailed description of a typical case is the following: *Case No. 28*, Business man, 55 years old, married. Before the onset of the disease he had shown no peculiar symptoms. He had adjusted himself well socially and had been able to work up a fairly big business. His illness began in 1950 without any apparent reason. His complaints were a peculiar constricted feeling in the scalp; he felt restless, nervous, anxious and discomforted. He gave up social life and made his wife control his business. He passed most of the time in his home feared to go out, isolated himself more and more, became increasingly pre-occupied by his neurotic symptoms and feared he would die. He consulted several well-known doctors, but all were unable to help him. During 1952 and the first half of 1953 he was submitted to an intense psycho-analytical treatment by a well-known psychiatrist, but no improvement was seen.

The treatment was begun on October 20th with placebo tablets and continued until November 20th. Possibly a slight subjective improvement was felt by the patient during this period, but he still took barbiturates in the evening and tinct. opii during the day. On November 20th the placebo tablets were replaced by Suavitil, at first 0.5 mg 3 times daily, later 3 mg daily. After about 2–3 weeks a considerable improvement was seen. He was able to work in his office, at first 3 days a week, later for longer periods. He was able to drive his car again and could visit the doctor without being accompanied by his wife. He declared in January 1954 that his state was "fifty-fifty". His wife, who has been interviewed several times, states that his improvement is completely evident since the beginning of treatment (except during the first weeks, when he received placebo tablets, unknown also to his wife). However, the state oscillates somewhat, small relapses are seen

TABLE 1

Diagnosis	Age	Duration of the disease	Previous treatment and main symptoms	Duration of treatment with suavitil	Dosage	Result of treatment
Pt. No. 27. Psychoneurotic disorder (mixed type).	33 ♂	1½ year	Anxiety, tension, depressive periods, hypochondrical complaints, restlessness. (No other treatment previously).	9 months (2 periods with placebo, each of 1 month).	1.5 mg 3 times daily.	Moderate effect on the tension and anxiety. (Relapse in the placebo periods).
26. Psychoneurosis with somatic symptoms, affecting the circulatory system.	30 ♂	5 years	Palpitations, rapid pulse, feeling of agony, enormous anxiety, unable to work. (Previously treated with psychotherapy and ECT without effect).	1 month (No period with placebo).	1.5 mg 5 times daily.	Moderate effect on the pulse rate and the feeling of anxiety.
28. Psychoneurotic disorder (mixed type).	55 ♂	4 years	Constricting feeling in the scalp, restlessness, anxiety, fear to die, unable to work. (Previously intense psychoanalytical treatment without any improvement).	1 year (Placebo was given during 1 month at the beginning of treatment).	As indicated in Table 2.	(Good; now able to work, the anxiety less pronounced. (No effect of placebo).
4a. Psychoneurotic disorder (mixed type).	44 ♀	3 years	Anxiety, tension, restlessness, depressive state, hypochondrical complaints. (Previously treated with individual psychotherapy and ECT without effect).	3 months (Placebo was given 1 month at the beginning of the treatment).	1 mg 3 times daily.	No effect.

with somatic symptoms, affecting the digestive system.	♀	orism, nausea, vomiting without objective manifestations, restlessness, discomfort, feeling of tension. (Previously treated with individual psychotherapy and group therapy with only slight effect).	given 1 month at the beginning of the treatment).	3 times daily later 1.5 mg 3 times daily.	and nausea, no feeling of tension. (No effect of placebo).
30. Obsessive-compulsive reaction.	27 ♀	Depressive reactions, obsessive symptoms, anxiety for sharp and pointed objects, complaining of disorganized thinking. (Previously treated with psychotherapy, ECT, and insulin coma with only slight effect).	4 months (Placebo was given the first 3 weeks).	1 mg 3 times daily.	Moderate effect on the obsessive symptoms. (No effect of placebo).
7a. Obsessive-compulsive reaction.	35 ♀	Agoraphobic symptoms predominate, further feeling of agony and anxiety. (Previously treated with psychoanalysis without effect).	3 months (No period with placebo) Stopped medication on own initiative.	1 mg 3 times daily.	Moderate effect on the obsessive symptoms. No relapse after discontinuation of the medication.
25. Obsessive-compulsive reaction.	29 ♂	Predominate monosymptomatically, thinking that an evil smell leaves him in forms of flatulence, unable to work of this cause. (Previously treated with insulin coma without effect).	13 days (No period with placebo).	1 mg 3 times daily 10 mg daily the last 5 days.	No effect.

TABLE 1 (cont.)

Diagnosis	Age	Duration of the disease	Previous treatment and main symptoms	Duration of treatment with suavitil	Dosage	Result of treatment
24. Obsessive-compulsive reaction.	24 ♂	since the childhood	Predominate symptoms: the feeling, that he loses his hear and that he is going to be bald. Sleeping in strange compulsive positions. (Previously treated psychoanalytically without effect).	10 days (No period with placebo).	5 mg 3 times daily.	Slight, mainly sedative effect.
31. Psychoneurotic disorder (mixed type).	27 ♀	2 years	Afraid of becoming pregnant, sexual problems in her marriage, nervous, hypersensitive and misanthropic. (Previously treated with psychotherapy with some improvement).	4 months (Placebo was given in the first 5 weeks).	1 mg 3 times daily.	Uncertain effect. (The condition was changing much from period to period during the treatment).
23. Neurotic-depressive reaction.	27 ♂	5 years	Depressive symptoms, feeling of inhibition and difficulties to think, complained of voices within his head, lack of initiative and restlessness (serious attempt to commit suicide ½ year before the treatment with Suavitil). (Previously treated with ECT and insuline coma in the depressive periods with some effect)	2½ months (No period with placebo).	1.5 mg 3 times daily.	Good effect on the feeling of inhibition and the depressive symptoms.

33. Neurotic-depressive reaction.	70 ♂	2 years	Depressive and obsessive symptoms, lack of initiative, difficulties to sleep. (Previously treated with opium, malononitrile and oestrogens with only slight effect).	5 months (Placebo was given 1 month at the beginning of the treatment).	3 times daily.	1 mg 3 times daily later 1.5 mg 3 times daily.	Moderate sedative effect, less excited. (No effect of placebo).	1 mg 3 times daily. (No effect of placebo).
34. Psychoneurotic disorder (mixed type).	30 ♀	1 year	Always sensitive, more and more depressive, afraid of becoming insane, excited and extremely psycholabile. (Previously treated with ECT and insuline coma with only slight effect).	3 months (Placebo was given the first 3 weeks of treatment).	1 mg 3 times daily later 1.5 mg 3 times daily.	1 mg 3 times daily a short period 1.5 mg 3 times daily.	No effect.	1 mg 3 times daily. (No effect of placebo).
29. Psychoneurosis with somatic symptoms.	60 ♀	6 years	Pains in parotid region, no organic base for the complaints. (Previously treated with excision of left auriculotemporal nerve and local anaesthetics in the trigeminal nerve without effect).	1½ month (Placebo was given the first 2 weeks of treatment).	1 mg 3 times daily a short period 1.5 mg 3 times daily.	1 mg 3 times daily a short period 1.5 mg 3 times daily.	No effect.	1 mg 3 times daily. (No effect of placebo).
15a. Hysterical reaction.	34 ♀	2 years	Multiform hypochondric complaints, excited, and psycholabile.	5 days (No period with placebo).	1 mg 3 times daily.	1 mg 3 times daily. (No effect of placebo).	1 mg 3 times daily. (No effect of placebo).	1 mg 3 times daily. (No effect of placebo).

TABLE 2

Date from	Week number	Dosage	Side-effects	Clinical notes
1953 Oct. 20	1	<i>Placebo</i> , 2 tablets 3 times daily.	no	Unable to work, anxious, restless, constricted feeling in the scalp. States: perhaps feels better.
	2	do.	no	Unchanged as above.
	3	do.	no	Unchanged as above.
	4	do.	no	Unchanged as above.
Nov. 20	5	<i>True tablets</i> 0.5 mg 3 times daily.	slight dizziness	Unchanged as above.
Nov. 27	6	1.0 mg 3 times daily.	dryness in mouth	Feels quieter. No further clinical effect.
Dec. 4	7	do.	no	Works 3 days this week. Less anxious and restless.
Dec. 11	8	0.5 mg + 1.0 mg + 1.5 mg	slight dizziness	Works 3 days this week, subjective complaints less pronounced.
Dec. 18	9	do.	no	As above. The patient summarizes, 40 % of "my time" is good, 60 % bad.
Dec. 25	10	do.	no	Happy to work.
1954 Jan.	11-14	1.0 mg + 0.5 mg + 1.5 mg	no	"50 % good and 50 % bad".
Febr.	15-18	do.	no	Working 4 days weekly from 9 a.m. to 5.30 p.m.
March	19-23	1.0 mg + 0.5 mg + 1.5 mg	no	Gives up isolation. Contacts friends and business relations.
April		do.	no	For periods constricted feelings in the scalp, but less than before medication. Working regularly.
May- Sept.	-48	do.	no	Status September 1954: Quieter, less anxious and tense. Working 4-5 days a week, less isolated. For periods still constricted feelings in the scalp.

in connection with infections, such as colds and attacks of gout, from which he suffers. In spite of such small relapses, he is able to travel alone and visit his customers, and in May he made a business trip of several days' duration. *Table 2* shows the progress of the patient as noted from week to week during the treatment.

DISCUSSION

The patients mentioned in this report are the first patients to have been treated with Suavitol, and the experiment gives only a rough orientation as to the clinical usefulness of the drug. The patients tested have represented a wide range of mental diseases, and all patients brought under treatment are included in this report.

In spite of the limited number of patients, the investigation gives certain hints as to the field of indications for the clinical use of Suavitol.

No or little beneficial effect could be obtained in the 22 psychotics. This naturally does not exclude the possibility that psychotics with other symptoms than those described here can be beneficially influenced by this drug. More encouraging results were obtained in the treatment of the psychoneuroses. From *Table 1* is seen that the clinical state was improved in 10 of the 15 patients treated. The effect was slight in one (No. 24), moderate in 6 (Nos. 27, 26, 30, 7a, 33, 34) and marked in 3 cases (Nos. 28, 32, 23). No effect was seen in 4 cases (Nos. 4a, 25, 29, 31). In one patient (No. 15a) the state deteriorated.

Some of the earlier patients (Nos. 26, 25, 24) have not been followed up, and it is possible that more clear cut results could have been obtained with the later more elaborate experimental technique. The experimental technique and the choice of the patients eliminate the effect of a suggestion almost with certainty. Spontaneous remissions are seen in these diseases, but the probability is very small that all the improved patients would show spontaneous improvement at the same time as the Suavitol medication was begun, or placebo tablets were replaced by test tablets. The effective dose seems to be 3–4.5 mg daily divided in 3 doses. Doses of 1.5 mg daily have only in very few cases given slight side-effects.

None of the patients treated with Suavitol have been completely freed from their neurotic symptoms, but a number of them, especially those with obsessions or psychosomatic symptoms, have declared spontaneously that their symptoms did not trouble them as much as before. This description of the effect appears similar to the effect of lobotomy, and it may possibly be of importance in the theoretical evaluation of the drug's mode of action. However, in this connection the negative effect of Suavitol on the case of intractable pains (No. 29) must be borne in

mind. There is no analgesic effect, and no euphoric effect, as after morphine or the synthetic morphine like drugs, have been observed. Neither have we seen even the slightest sign of addiction: the patients are not inclined to increase their doses, and no abstinence symptoms have been noted after discontinuing medication.

The material is far too limited to give any indication as to the form of psychoneurosis in which a beneficial effect can be expected. Two patients with apparently similar symptoms (e.g. No. 32 and No. 4 a) can be very different in their reactions, and a thorough analysis of a long series can perhaps alone make it possible to distinguish between reactive and resistant clinical types.

The duration of the result is still an open question. Some patients (e.g. Nos. 27, 28 and 32) have been treated continuously for more than 8 months without any sign of a decreasing effect. Another question is for how long an effect will last after discontinuing medication. Here it may be mentioned that it has generally been some days before the symptoms have slowly reappeared when true tablets have been replaced by placebos, and in some patients (e.g. No. 7 a) the improvement seen after medication has persisted at least for some months after discontinuing medication. In them the effective compound has been eliminated from the organism long before the reappearance of the symptoms, and the effect, if really due to the medication has thus been more than mere symptomatic. In other cases the symptoms have reappeared almost immediately the Suavitil has been eliminated from the organism. The effective duration of a medication is probably dependent on the nature of the case and can only be determined by further investigations.

The last important question still to be answered is whether or not better results can be obtained if the Suavitil medication is combined with psychotherapy or perhaps with the use of other drugs. In the present investigation, aiming at evaluating the "pure" effect of Suavitil, no attempt has been made to solve this problem, but in cases from another source it is reported that the medication facilitates the psychic contact between patient and therapist.

SUMMARY

Some preliminary clinical experiments with a new type of sedative, Suavitil, are described. Various types of psychoses (schizophrenia, paranoia, endogenous depression) were as a whole uninfluenced by the treatment. Of 15 cases of psychoneuroses, 10 showed an improvement simultaneously with the onset of medication. Placebo tablets were without effect in these patients.

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RECORDING OF THE SKIN RESISTANCE IN THERMAL AND ROTATORY STIMULATION OF THE LABYRINTH

By

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Both neurologists and otologists encounter many patients who complain of vague sensations of vertigo and susceptibility to changes of position. Conventional otoneurological examination usually reveals no abnormal vestibular reactions, but nausea, cold sweats, etc., are not infrequently found after thermal and rotatory stimulation, even with the use of stimuli which in "normal" patients are usually too weak to elicit such reactions. The question thus arose in what degree a closer study could be made of these vegetative phenomena which, though of uncertain clinical significance, seemed worth while recording.

A study of the literature revealed that many investigators had been concerned with the same problem. In 1922, *Spiegel* and *Démètrides* demonstrated that vestibular stimulation in experimental animals produced a fall in blood pressure. Their experiments have since been repeated and modified by a large number of workers evidently partly in the hope of elucidating the vertigo associated with asthenia, head injuries, etc. (*cf. Streiff & Monnier* 1942, *Montandon* 1943). Substantially the following facts have emerged. In animal experiments there occurs, at all events under some forms of narcosis, a fall in blood pressure (with reduction of the retinal arterial pressure and cerebral vasoconstriction), whereas the heart rate is not so regularly influenced; the respiration may be retarded, the intestinal peristaltic movements increased, and the stomach contracted. *Gernandt* and *Schmiterlöw* (1953) found, it may be added, that these initial vegetative reactions were counteracted by certain antihistaminics, and they attributed them to an effect on the vagus.

In human beings the reactions are far more difficult to study. Non-

specific effects of an emotional character occur; there may be blood-pressure elevation and tachycardia, and likewise altered respiration, peristaltic movements, and so on. *Streiff, Montandon and Monnier* (1943) reported that stimulation of the labyrinth in some susceptible persons was attended by a prolonged rise of pressure in the homolateral retinal arteries. This rise was preceded by a fall of short duration; and since the cerebral arteries were thought to react in the same way, special clinical interest might attach to the reaction. The method is somewhat cumbersome, and in any case it is not serviceable for routine use.

We sought instead to study the nausea by recording the skin resistance. *Hemmingway* (1944) and *Diamant* (1953) had previously made use of the skin resistance in determining the onset of sweating in motion sickness produced experimentally by the parallel swing.

The only author who appears to have studied skin resistance in conventional stimulation of the labyrinth is *Bijtel* (1943), who laconically reported that it was not changed.

METHOD

Variations in skin resistance can be demonstrated with a fairly simple commercial apparatus for resistance measurements; and for rough clinical determinations it may suffice merely to read the deflection registered by an apparatus of this type - which deflection is usually substantial at the onset of sweating. This procedure does not, however, enable a closer study to be made of the variations in resistance; some recording device must be employed.

The following methods of measuring the skin resistance and of recording its variations was developed with a view to obtaining a relatively simple and easily operated recording machine with satisfactory electrical stability. *Behr* designed a similar apparatus for studies of the psychogalvanic reflex; the present device is designed for use where greater and more prolonged variations in resistance occur.

To the subject's forehead are applied, by means of a rubber band encircling the head, two electrodes consisting of a number of slender silver wires about 2 cm long, stretched parallel across bows about 1 cm wide.—The electrodes were thus designed in order that the evaporation of moisture from the skin surface would not be appreciably impeded. (In some experiments we used, in place of them, finger electrodes as in measurement of the psychogalvanic reflex.)—The electrodes are connected to a bridge, balanced by means of a rotary potentiometer. The resistance between them can be determined from a calibration curve. With any change in the skin resistance the balance of the bridge is disturbed, the resulting potential being conducted, via a contact, to an amplifier and recording apparatus. The contact

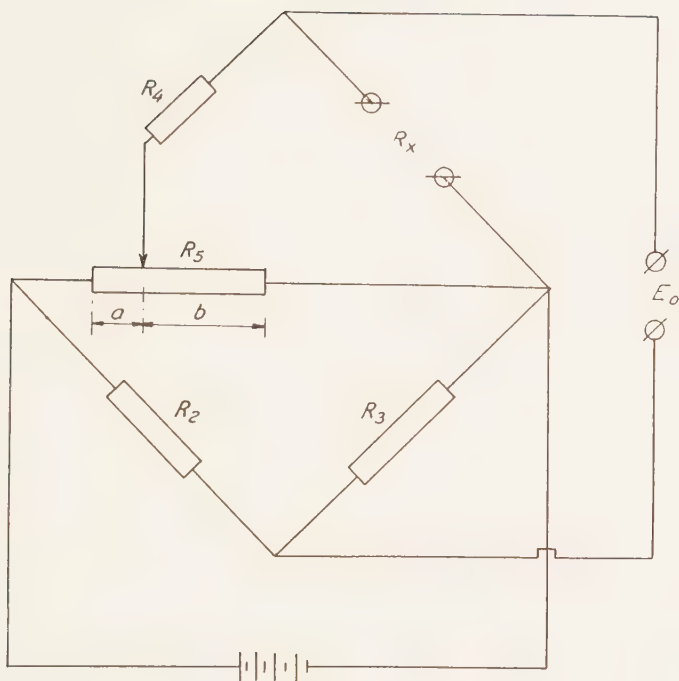


Fig. 1.

(impulse producer) closes the circuit for about 0.02 seconds once per second. In this way the variations in resistance are recorded as a series of impulses the amplitude and polarity of which are determined by the relative change in the skin resistance. —It was found to be of major importance to keep the potential between the electrodes below 0.2 volts; at higher potentials there was a tendency towards drifting, *i.e.* the skin resistance fell continuously for several hours. With the arrangement described here the resistance was virtually constant after about five minutes.—The mode of action of the bridge is shown in fig. 1, from which the switches for effective parts of the scale, etc., have been excluded in order to simplify the diagram. A zero potential indicator is connected to contacts R_x . The bridge is balanced by moving the arm of the potentiometer to a position where no potential is obtained between contacts E_0 . Provided the resistance in R_4 is high in relation to that in potentiometer R_5 , the following equation will be valid when the bridge is in equilibrium:

$$R_x \equiv \frac{R_4}{\frac{b}{a+b} \cdot \frac{R_2 + R_3}{R_3} - 1}$$

If, after balancing the bridge, the resistance of the object of measurement be changed from R_x to R_{x1} , a potential will result between contacts E_0 that will be directly proportional to the relative change in the resistance, regardless of the initial resistance of the object.

to the subject; when a certain angular velocity has been reached the rotation is continued for a while at a constant rate (maximum 60 degrees per second), then suddenly stopped and the duration of the post-rotational nystagmus and vertigo measured. The skin resistance was recorded via special contacts in the turning chair. It soon became evident, however, that it would be simpler and better to study the skin resistance at thermal stimulation according to Hallpike's standard method (irrigation of the ear for 40 seconds with 100 cc water at temperatures of 30° and 44° C). We investigated a total of about fifty subjects, the majority with thermal stimulation alone. Most of them were selected from patients who complained of vertigo and susceptibility to changes of position, usually of a moderate degree.

RESULTS

1. In these experiments there may occur nonspecific variations in resistance, occasionally very pronounced, though usually small. If the electrodes be placed on the finger tips as in recording the psychogalvanic reflex, and the apparatus then adjusted to a relatively high amplification, variations in resistance will be found in most persons. When we investigated such reactions to cupulometry, we found that in some persons even the slightest sensation of rotation during the acceleration was attended by minor falls in resistance and that very pronounced reactions might appear when the rotation was stopped. (One of the original purposes of our experiments was, with the aid of the psychogalvanic reflex, to objectivize the after-sensations at cupulometry). One of us was found to have a very regular curve during rotation (often with some increase in the resistance), but when rotation was stopped he invariably showed a distinct fall in skin resistance - a fall that did not disappear or decrease even after repeated experiments. The cause of this decrease is obscure; it may, of course, be attributable to a nonspecific reaction, but if so then the reaction might well be expected to subside in a trained subject, as occurred in Hardy, Wolff and Goodell's pain experiments.

2. When electrodes of the aforementioned type were applied to the forehead and the amplification reduced, the resistance curve was stabilized after about five minutes, and the resistance fell during the experiments but little initially, even if these susceptible patients were subjected to such unpleasant procedures as the insertion of a tube into the ear, irrigation with cold or warm water, and to nystagmus with vertigo. Naturally there were a few exceptions in which already those stimuli produced a marked fall in the skin resistance, in some cases

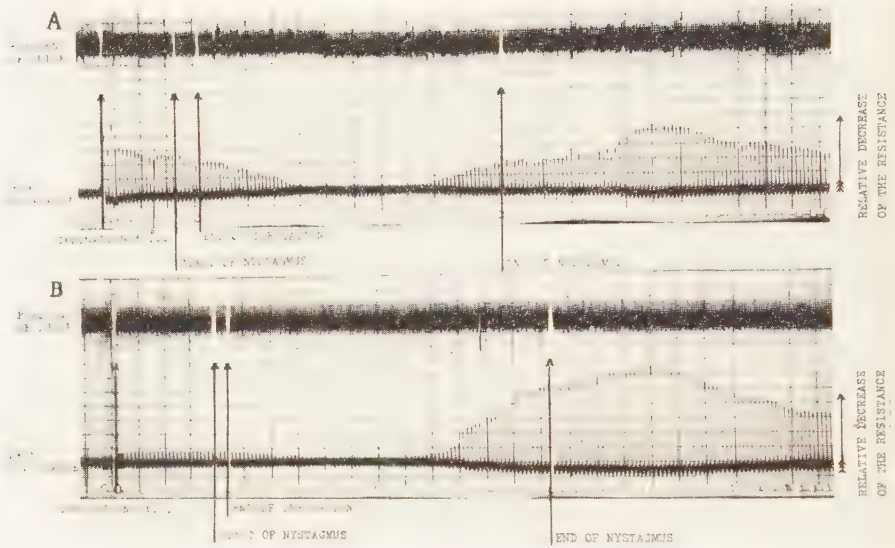


Fig. 3. — = 10 seconds
Decrease of skin resistance after thermal stimulation.

bordering on cold sweats. Figure 3 A shows a moderate initial fall in resistance on thermal testing.

3. At thermal stimulation the majority of patients after 2–3 minutes—or roughly just when the the nystagmus had subsided—and following an initially stable resistance, presented a reaction consisting of slight nausea associated with a more or less pronounced fall in the skin resistance. Fig. 3 B shows the same case as in Fig. 3 A; at this second test the patient only exhibited an inappreciable initial fall and then the characteristic secondary fall.

In strong reactions this fall sometimes appeared somewhat earlier, though it always seemed to reach its maximum some minutes after the start of irrigation. Mostly it was of a few minutes' duration, and usually there was coincident subjective nausea. The reaction also occurred in persons who showed no signs of apprehensiveness—for example, hospital staff members who had undergone several tests. In some cases the subjective reaction was slight and the tendency towards nausea would have been doubtful had it not been objectivized by the fall in skin resistance. The latter often fell considerably, without any distinct appearance of moisture on the forehead—evidently because of increased intracutaneous fluid.

4. We also conducted experiments on a patient with a severe post-concussional syndrome who showed very high susceptibility, with pronounced nausea and sweating at both thermal and turning tests. When

Amobarbital Sodium was administered intravenously, approximately as in narcoanalysis, he was quite unconcerned during the irrigation, and indeed he was highly amused by the apparent rotation of the room during the nystagmus phase. When the dizziness subsided after about three minutes he began to complain of nausea, and coincidentally there was a moderate fall in the resistance. At the end of the experiment he was still very much under the effect of the drug. The semi-narcosis obviously lessened the tendency towards nausea, yet the experiment demonstrates that euphoria during the nystagmus phase does not necessarily prevent the occurrence of nausea.

DISCUSSION

Susceptible patients thus, after a fairly characteristic latent period, show a nausea that may be mild but that may sometimes become very marked, with a vomiting tendency. Usually the nausea is of short duration, but in some cases slight nausea persists for some considerable time. We obtained an objective measure of this by recording the variations in skin resistance, which could be studied effectively with the method employed. However, it must naturally be taken into account that the parallelism between the subjective condition and the variation in skin resistance is not complete; for instance, there are individual variations in the sweating tendency.

We have nevertheless interpreted the reaction as a characteristic result of stimulation of the labyrinth, even though the degree of apprehensiveness naturally influences the severity of the response. This emotional influence can scarcely be avoided in non-anesthetized patients. The same difficulty is frequently encountered in the investigation of vegetative reactions in man, as for example in studies of seasickness.

The clinical significance of the vegetative vestibular reactions, as pointed out in the foregoing, has been discussed in the literature. Human subjects, like laboratory animals, can probably be expected to show initial vegetative reactions, whereas the nausea is a relatively late vegetative effect. At all events it is not impossible that such patients as react with marked nausea to vestibular stimulation will show slight vegetative reactions even to minor rotatory movements of the head—and this might be one of the explanations of their vertigo. More detailed studies are of course required before any definite conclusions can be reached in this respect.

SUMMARY

The present investigations were designed, by graphic recording of the variations in skin resistance, to throw further light on the nausea

associated with sweating, etc., that may attend rotatory and thermal vestibular stimulation.

A specially designed apparatus was employed for recording. About fifty patients were investigated.

Vertigo induced by slight rotatory stimulation (cupulometry) was sometimes accompanied by a fall in skin resistance that was difficult to distinguish from nonspecific falls due to emotional factors.

Thermal stimulation often, after a latent period of 2-3 minutes, produced a pronounced fall in skin resistance coincidently with nausea. The fall sometimes appeared without demonstrable sweating or other objective signs of nausea.

The causes of this evidently characteristic fall in skin resistance are briefly discussed. The method employed here seems to be serviceable as a simple means of recording vegetative vestibular reactions.

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PHAECHROMOCYTOMA ASSOCIATED WITH NEUROFIBROMATOSIS

By

JOHN RIISHEDE

Neurofibromatosis and phaeochromocytoma were both described about seventy years ago. Neurofibromatosis has been wellknown since v. Recklinghausen described it in 1882 (15), whereas the knowledge of the clinical and physiopathological features of phaeochromocytoma has been but slowly progressing. Not until the last two decades has attention been particularly called to this condition. The pathoanatomy of a phaeochromocytoma was first described by *Fränkel* (4) in 1886. The relation between its pathoanatomical and clinical manifestations was established by *Labbé et al.* in 1922 (8). The first surgical removal of a phaeochromocytoma after a correct preoperative diagnosis was made, was reported by *Shipley* (19) in 1929. The presence of a pressor substance in the blood stream during hypertensive paroxysms was demonstrated by *Beer, King and Prinzmetal* (1) in 1937. Since that time, further development has been characterized by progressing knowledge of the pathophysiology of the disease, improved diagnostic methods, and, finally, by better results of treatment due to advances within the fields of surgery and anaesthesiology.

The combination of phaeochromocytoma and neurofibromatosis was described for the first time by *Suzuki* (cited by *Glushien et al.* (6)) in 1910, i.e. before the clinical signs of phaeochromocytoma were known, and since that time 19 cases of this combination, including seven since 1950, have been reported.

An additional case of phaeochromocytoma associated with neurofibromatosis in a patient whose only symptom was migraine, is reported below.

CASE REPORT

The patient (F 15328) was an unmarried woman, aged 26, who was admitted to this clinic with migraine on August 8, 1953.

Her mother had suffered from attacks of headache accompanied by vomiting, and a brother had similar attacks of headache without vomiting. There were no cases of skin affections or known instances of hypertension in the family.

In her childhood the patient had suffered from attacks of headache, often accompanied by vomiting. In her adolescence the attacks became less frequent, but during the last two years prior to admission she had suffered from constant right-sided headache. Violent aggravations had occurred, lasting from two to eight days and being accompanied by dysphoria, hypersensitivity to noise, vomiting, polydipsia, and polyuria.

During the last 4–5 years before admission numerous small nodules had developed in the skin of the face, of the trunk, and of the extremities. The skin had become spotted with areas of brown pigmentation. Two years before admission a nodule on the chin had been removed, but it had soon grown out again to its former size.

Otherwise, her past history was that of good health; she had menstruated regularly and never been pregnant.

Physical examination revealed a woman of normal body build and state of nutrition, without signs of endocrine dysfunction. Her intelligence was normal, but she gave the impression of being mildly depressed. A neurological examination showed normal conditions. Ophthalmoscopy revealed somewhat narrow and shining arteries, but the optic discs were normal, and so were the fields of vision. Ear examination showed unimpaired hearing and normal vestibular function. A mild dysrhythmia was disclosed in the EEG with no focal changes. There was no enlargement of the thyroid, and no signs of increased blood-flow through this gland could be demonstrated. The pulse rate at rest was between 80 and 90. The heart was normal to auscultation, except for a blowing systolic murmur over the entire precordium. The electrocardiograms were normal with a slight left-axis deviation, and roentgenograms of heart and lungs likewise showed normal conditions. The abdomen was soft without palpable tumours. The urine did not contain abnormal elements, and its specific gravity was normal. The skin was slightly seborrheic, and on the trunk there were numerous café-au-lait spots ranging in diameter from a few millimetres to 5–6 cm and multiple subcutaneous soft tumours of a diameter of up to 10 mm. In the face and on the extremities there were a few slightly larger tumours, some of which were covered by bluish skin. One of these nodules was removed for histological examination, which showed a typical neurofibroma.

On admission, the blood pressure was 200/140 mm Hg. Two days

later the reading was 210/160, but afterwards the pressure fluctuated around 160/110, with the highest readings on the lower extremities. The patient was suffering from constant right-sided headache, which could be relieved by intravenous injections of ergotamine, but the intensity of the headache seemed to be unrelated to the blood-pressure level. Massage of the right renal region gave an increase in blood pressure from 150/110 to 190/140, but this increase failed to develop when massage was preceded by an intravenous injection of 5 mg of Regitine, whereas the same intravenous dose of the drug did not bring about any fall in the blood pressure at rest. A test with 0.025 mg of intravenous histamine did not result in a rise in blood pressure.

The haemoglobin level, the leukocyte count, and the differential count were within normal limits. The Wassermann reaction in blood and spinal fluid was negative. Blood urea, serum bicarbonate, serum chloride, and serum protein showed normal values. The protein content of the spinal fluid was slightly increased, but there was no increase in the cellular content. Fasting blood sugars were 110, 118, 95, and 99 mg %, and the basic metabolic rate was slightly increased with values of 124, 117, 119, and 114 mg %. The cholesterol content in the serum was normal. The 24-hours excretion of 17-ketosteroids in the urine did not deviate from the normal, whereas the corresponding excretion of adrenaline and noradrenaline was markedly increased with values of 554 and 490 μ g per 24 hours, of which noradrenaline constituted more than 90 %.

A gynaecological examination revealed normal conditions, and intravenous pyelography did not show any abnormalities. Retroperitoneal insufflation of 1000 ml of oxygen according to the technique of Ruiz Rivas resulted in very distinct visualization of both adrenals, the right measuring 14×7 cm and the left 5×6 cm. The changes were very conspicuous in tomograms taken in the recumbent position.

Following preoperative treatment with adrenocortical extract, the patient was subjected to operation in the Department of Surgery of Aarhus Municipal Hospital (Professor V. Aalkjær). Through a trans-thoracic approach a tumour weighing 24 g was removed from the right adrenal. Histological examination showed a typical pheochromocytoma. The tumour tissue had infiltrated and destroyed the surrounding adrenal cortex, but did not otherwise show signs of malignancy. It contained 144 mg noradrenaline and 18 mg adrenaline. A cutaneous neurofibroma, weighing 1.2 g, which was removed at operation, did not contain demonstrable amounts of adrenaline or noradrenaline.

By intravenous administration of Regitine the blood pressure was kept fairly constant during the operation and did not exceed 190/140.

Because of a fall in blood pressure to 125/90 after the removal of the tumor noradrenaline was given in intravenous drip infusion during the first postoperative hours. Apart from this, the postoperative course was uneventful, and the blood pressure level rapidly became stabilized between 140/100 and 125/80. Fasting blood sugars were around 80 mg %, and a fortnight after the operation the excretion of adrenaline and noradrenaline in the urine had fallen to 80 μ g per 24 hours. The levels of serum potassium and serum sodium were also normal. A week after the operation the headache had disappeared, and the patient was discharged on the 18th postoperative day.

Three months later, the patient was readmitted for follow-up. She had been able to work as a housemaid for the last two months. She felt well and had not had any attacks of headache since discharge. The blood pressure was 100–110 systolic and 70 diastolic, but might occasionally—when she felt nervous or anxious—rise to 160/110. The basic metabolic rate was 101–105 %. Fasting blood-sugar values and glucose-tolerance curves were normal, and the 24-hours urinary excretion of noradrenaline was 91 and 78 μ g, while that of adrenaline had fallen to zero.

DISCUSSION

The past history of this patient did not differ markedly from that of an ordinary migraine. Some of her relatives suffered from paroxysmal headache, and her own had persisted since early childhood. There was no feature in her history that might arouse suspicion of paroxysmal hypertension, and the attacks of headache had never been accompanied by pallor, sweats, cool and clammy extremities, increased heart action, salivation, or dilatation of the pupils. During the hospital stay no relation could be demonstrated between the exacerbations of headache and the height of the blood pressure, and ergotamine relieved the headache without causing changes in the blood pressure. These findings suggested that her headache was an ordinary migraine, which was unrelated to the pressor effect of noradrenaline. The disappearance of the headache after the removal of the phaeochromocytoma and the concomitant return to normal, *inter alia*, of the noradrenaline content of the blood do not justify the assumption of a causal relationship between the two conditions. As in the case of other diseases phaeochromocytoma may besides its organic manifestations display signs and symptoms that may be taken as being psychogenic in nature, for example headache. The beneficial effect of extirpation on the headache might then be explained by the "unspecific" psychic effect

of such a major operation or by changes in the life of the patient which the operation might entail. This patient actually had an emotional conflict, which was solved shortly before her second admission, but her headache had commenced many years before this conflict arose and it disappeared a couple of months before its solution, and apart from the period of convalescence the life of the patient with regard to working conditions and environment was exactly the same after the operation as before. Thus, the assumption of a psychogenic origin of the migraine can scarcely be maintained.

Probably both a hereditary constitutional factor and an unspecific accessory one are of importance for the development of migraine. This has been maintained by a number of clinicians, among others by *Munch-Petersen* (13). On this hypothesis the constitutional factor should make it possible for incidental somatic or psychic affections, such as anaemia, a metabolic disorder, muscular infiltrations, a neurosis, or a depression to produce migraine. This theory is supported by the common clinical experience that successful treatment of such an affection in a patient suffering from migraine will also often eliminate the migraine—and that the latter may recur if other psychic or somatic diseases develop in the patient.

In our patient it was reasonable on the basis of her past history to assume the presence of such a constitutional factor; and, moreover, the phaeochromocytoma represented several possible accessory factors due to the interference of the noradrenaline with various somatic processes.

Based on our present knowledge of the pharmacological actions of ergotamine and noradrenaline it is difficult to explain the effect of the former on the headache. Noradrenaline, which was predominant in the secretion of the phaeochromocytoma, produces vasoconstriction—also intracranially—and a rise in blood pressure; and this also applies to ergotamine, but this drug may abolish many of the effects of the adrenaline group, e.g. that of vasoconstriction. In fact it was the knowledge of this antagonism which in 1937 put *Beer et al.* (1) on the track of the adrenaline in the pressor substance which they demonstrated in the blood of a patient with a phaeochromocytoma. Finally, in animals treated with ergotamine, adrenaline may produce effects which are the exact reverse of those usually encountered: for example, vasodilatation instead of vasoconstriction (14). Thus the pharmacodynamic conditions are extremely complicated and at present they can scarcely be made to conform with the current theories as to the pathophysiology of migraine.

The diagnostic procedure employed in the present case followed

the usual lines, i.e. in the first place to establish the presence of a phaeochromocytoma and, secondly, to disclose its localization.

The presence of constantly increased, but fluctuating blood pressure in a young individual, without aortic stenosis or renal disease would immediately lead one to suspect the nature of the condition. The mild hypermetabolism and the occasionally elevated fasting blood-sugar values enhance this suspicion. The presence of these three signs—hypertension, hypermetabolism and hyperglycaemia—should always be followed by a close search for a phaeochromocytoma, because of their frequency in this disease. The blood-pressure level was usually around 160/110, and rises to 210/160 were not accompanied by subjective or objective changes in her condition. The only “provocative” test performed was the stimulation with 0.025 mg histamine. This did not produce any rise in the blood pressure. Such “false” negative histamine tests have often been observed, among others in this clinic in a patient with Cushing’s disease and phaeochromocytoma (reported by *Faber* (3)). A test with tetra-ethylammonium bromide (T.E.A.) was not performed. According to *La Due et al.* (9), who introduced this test in 1948, it should be preferred to a histamine test, because it is claimed that the rise in blood pressure produced by T.E.A. in contrast to that induced by histamine can be controlled simply by tilting the patient into the upright position. These investigators observed the said reaction in a patient with a verified phaeochromocytoma. Since then, their recommendation of the test has been quoted in several papers, and the test has often been employed. However, perusing the literature I have been unable to find communications confirming their observation. In two previous papers, published in Danish (16, 17), I have emphasized that no theoretical basis exists for the advantage of T.E.A. over histamine as has been claimed by *La Due et al.* It is true that in patients without phaeochromocytoma T.E.A. usually induces a fall in blood pressure, which is enhanced if the patient is placed in the upright position. This drop in blood pressure may be overcome by administration of adrenaline. Qualitatively, the pressor substance—adrenaline-noradrenaline—secreted by a phaeochromocytoma is presumably the same whether the attack is precipitated by histamine, T.E.A., or otherwise. Accordingly, it cannot be expected that the blood pressure during an attack should respond appreciably to a change in position, or that the response to tilting the patient should be different in attacks precipitated by either of the two drugs. Nor does the theory advanced by *La Due et al.* hold in practice. In a case reported in one of the aforementioned papers (17), the patient responded to T.E.A. with a very violent attack of hypertension,

which persisted for two days and led to death. During the entire attack the blood pressure remained absolutely irresponsive to changes in the position.

An intravenous injection of 5 mg of Regitine did not lower the blood pressure, which was 160/105 at the beginning of the test. This is in keeping with the experience gained by *Gifford et al.* (5), viz. that "false" negative Regitine tests are not unusual at low hypertensive blood-pressure levels. On the other hand, the same dose of intravenous Regitine could prevent the rise in blood pressure which was induced by massage of the right renal region.

The adrenaline-noradrenaline assays of the urine and of the removed tumour were made according to the technique of *Lund* (10). The average excretion in normal individuals as measured by this fluorimetric method is approximately 50 μ g of adrenaline-noradrenaline per 24 hours, and is almost exclusively noradrenaline. A 24-hour excretion of at least 150 μ g may be regarded as an unquestionable sign of the presence of an endocrinely active phaeochromocytoma. In the case reported here, the 24-hour excretions were 554 and 490 μ g pre-operatively and 80, 91, and 78 μ g postoperatively. Normal adrenals contain a total of about 3 mg of noradrenaline and about 11 mg of adrenaline (11). The removed tumour weighed 24 g, i.e. twice as much as a pair of normal adrenals, but it contained about 50 times as much noradrenaline and about twice as much adrenaline as normal. Thus, there is agreement between the postoperative fall in the adrenaline-noradrenaline excretion and the postoperative clinical findings.

The second phase of the diagnostic procedure—the localization of the phaeochromocytoma—was not difficult in this case. Massage of the right renal region resulted in a definite increase in blood pressure, while this was not the case on the left. A retroperitoneal pneumography according to the method of *Ruiz Rivas* (18) gave a very distinct visualization of the adrenal tumour on the right side.

The combination of phaeochromocytoma and neurofibromatosis has been described previously. In reviewing the 165 cases of phaeochromocytoma on record *MacKeith* (12) in 1944 found nine cases associated with neurofibromatosis. In 1953 *Glushien et al.* (6) reported an additional case and stated that the combination had been observed in a total of 18 instances. Their review includes cases up to the end of 1951. In 1952 *Koonce et al.* (7) published a case of bilateral adrenal phaeochromocytoma associated with neurofibromatosis; together with the present one this combination has thus been recorded in a total of 20 instances.

The number of cases of phaeochromocytoma published up to the

present amounts to about 300. The association with neurofibromatosis occurred in 6 per cent. of the cases on record. Considering that both diseases are rare, this would seem more than coincidental. It should be recalled, however, that the figures are small, so that nothing can be said as to the actual frequency of this combination. The proportion between recognized and actually occurring cases of phaeochromocytoma with and without neurofibromatosis is unknown. Nor do we know anything about the ratio between the numbers of observed and published cases. The considerations of *Glushien et al.* (6) on the relation of phaeochromocytoma to the neurocutaneous syndromes (neurofibromatosis, von Hippel-Lindau's syndrome, tuberous sclerosis and Sturge-Weber's disease) are interesting, but owing to the small and unreliable figures they can for the present be regarded only as lines of further research. A possible relationship between phaeochromocytoma and neurofibromatosis cannot be rejected, simply because both the chromaffine cells of the phaeochromocytoma and the specific elements of the neurofibroma, the lemmocytes (*Del Rio Hortega*) are of ectodermal origin, both derived from the neural crest. *Von Euler's* demonstration of noradrenaline in peripheral nerves of cattle (2) would fit well into the theory, and so would a possible demonstration of noradrenaline in neurofibromata. However, I have been unable to find in the literature any such attempts. In the present case, it was impossible to demonstrate adrenaline or noradrenaline in a cutaneous neurofibroma weighing 1.2 g, i.e. the tumour contained less than 1 μ g of these substances.¹ So far there is reason to focus attention on these rare diseases and their interrelationship. Although, as a basis of inferences the figures mentioned above are unsatisfactory, they are so conspicuous as to require further investigation.

SUMMARY

A case is reported of phaeochromocytoma associated with neurofibromatosis in a 26-year-old woman suffering from migraine. The relation of migraine to the endocrine activity of the phaeochromocytoma is discussed, and the possible relationship between phaeochromocytoma and neurofibromatosis is mentioned.

The phaeochromocytoma was localized in the right adrenal and was removed by operation, after which the migraine disappeared.

¹ This analysis was performed by *Alf Lund*, Ph.D., of the Physiological Laboratory of Ferrosan, Ltd., Copenhagen.

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THE ELECTROMYOGRAM IN PERIODIC PAROXYSMAL PARALYSIS

By

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Periodic paroxysmal flaccid paralysis involving a few or several muscle groups has long been recognized as a well-defined clinical syndrome. Although a few cases of periodic paralysis had been reported earlier (*Cavaré*, 1853; *Romberg*, 1857; *Hartwig*, 1874; *Schachnowitsch*, 1882; *Gibney*, 1882); *Westphal*, in 1885, was the first to recognize the disorder as a distinct disease entity. In his description of the symptomatology, which is now so well-known that further description is uncalled for, *Westphal* calls attention to the complete unresponsiveness of the paralysed muscle both to direct and indirect electrical stimulation as a characteristic feature. A familial occurrence of the disease has been described by several authors (*Couzot*, 1886; *Schmidt*, 1919; *Janota* and *Weber*, 1928; *Gaupp*, 1940), but sporadic cases are encountered as well (see *Dalinghaus*, 1941).

It was early observed that the administration of potassium salts is therapeutically advantageous in this condition (*Singer* and *Goodbody*, 1901; *Mitchell*, *Flexner* and *Edsell*, 1902; *Holtzapple*, 1905), whereas in susceptible persons attacks can be precipitated by sugar, by insulin, and by adrenaline, all of which are known to produce a lowering of the serum potassium concentration (*Shinosaki*, 1926; *Yoshimura*, 1930). In 1934, *Biernond* and *Daniels* demonstrated that a fall in the serum potassium occurs during an attack.

More recently a number of studies have been carried out, primarily on the serum electrolytes, but also on the metabolism of muscle in this condition. Suffice it to mention here the investigations of *Aitken* and co-workers (1937), *Gammon* and co-workers (1939), and *Jantz* (1947), in whose papers further references will be found.

Gammon and co-workers found a fall in the serum potassium level during attacks, but emphasized that "there is no constant level of se-

rum potassium associated with transition from strength to weakness, nor from weakness to strength." However, "when the curve of serum potassium has been followed, the attack has developed with a falling, and the recovery ensued on a rising, serum potassium." They found no increase in the excretion of potassium in the urine prior to an attack, but on the other hand, a decrease, at the time of paralysis. This led them to conclude that the fall in serum potassium was due to a shift of potassium from serum to body cells. They maintained that the lowered serum potassium level *per se* is not an adequate explanation of the muscular weakness, because attacks had occurred with serum potassium within 10 per cent of the normal value and at a level which causes no weakness in normal subjects. They were of the opinion that the primary factor in this disorder is an abnormal demand for potassium in the affected muscles. *Danowski* and co-workers (1948), in conformity with the concept of *Gammon* and co-workers, found that during the development of paralysis potassium shifts from the extracellular to the intracellular phase with a resultant sharp decline in the extracellular potassium concentration. In contrast to *Gammon* and co-workers, *Aitken* and co-workers, as well as *Jantz*, found a definite correlation between the serum potassium level and the clinical symptoms. *Jantz* has given the normal serum potassium concentration to be 17–20 mg. per cent. He found that in mild transient attacks, accompanied by sensations of heaviness and weakness, reduced muscle reflexes, and slight loss of muscular power, the serum potassium level fell to 14–15 mg. per cent. In these cases the symptoms were most frequently confined to a few muscle groups. In cases of severe widespread paralysis, the serum potassium level varied between 5.5 and 13 mg. per cent. Normalization of the serum potassium level was paralleled by diminution of the paralysis. *Jantz* confirmed the finding of *Gammon* and associates that the urinary excretion of potassium is not increased during the attack. By biochemical analyses of biopsy specimens of affected muscle obtained at the time of paralysis and following recovery, he was able to demonstrate that the potassium content of muscle is raised considerably during a seizure, a finding that supports the concept of a shift of potassium from serum to muscle cells during a seizure. In addition, he noted that the urinary excretion of creatine in itself a pathological phenomenon—as well as the concentration of creatine in the blood were considerably decreased the day before an attack, and that the concentration of inorganic phosphorus in the blood was diminished at the time of paralysis. These findings led *Jantz* to conclude that periodic paralysis must be a primary muscular disease, and he propounded the hypothesis that the primary energy yield-

ing reaction in the metabolism of the muscle, namely, the break-down of phosphocreatine into creatine and phosphoric acid, is inhibited during an attack by potassium deficiency. This, in turn, is caused, not by external potassium losses, but by the change of potassium from free, ionized form to non-ionized form. This would also explain the therapeutic efficiency of potassium salts.

So far as we are aware, there has been, up to this time, only one electromyographic study in cases of periodic paralysis, namely, that by *Eichler, Jantz and Jung* (1940). In their study the peroneal nerve was electrically stimulated and the muscle action potentials led off from surface electrodes consisting of linen bandages moistened with saline solution. The action potentials were fed to an amplifier and recorded photographically from a cathode-ray oscilloscope. In the intervals between attacks the action potential response to low-frequency stimulation was normal. During an attack, however, the amplitude of the potentials was lower and the duration longer than normal—50 msec. as compared with about 15 msec. in normal muscle. They interpreted this phenomenon as a manifestation of retarded velocity of conduction of the impulses through the muscle fibres.

Since no analysis of the motor unit activity in periodic paralysis appears to have been published in the literature, it seemed worth while to report our observations in such a case.

METHODS

Concentric needle electrodes with an outside diameter of 0.5 mm were used. The action potentials were fed to a differential amplifier with a frequency response flat up to 5000 cycles per second. The decay time constant used was 1/25 sec. The amplifiers were connected to two double-beam cathode-ray oscillographs. One oscillograph carried no time marker and the beams were used for continuous recording of the action potentials, in order to obtain a general picture of the responses. The beams of the second oscillograph were set at an angle of 90 degrees to the first. One beam was used for recording at intermittent high sweep speed, to permit the study of detailed action potentials. The second beam carried a time marker. The cathode-ray tube tracings were photographed on film running at constant speed (about 7 cm/sec.).

CASE REPORT

G.B., a woman, aged 66. There was no known heredity for nervous diseases. Her past medical history was negative, apart from gall-bladder disorders for which cholecystectomy had been performed at the

age of 56. She had her first attack in 1949, with severe flaccid paralysis of both upper limbs for one or two days without pain or sensory disturbances. At that time she was admitted to another hospital. The lumbar spinal fluid was normal. The symptoms rapidly subsided and within 10 days she was fully restored. One year later she had a similar attack, although this time the paralysis was slightly less severe and disappeared within a week or so. Hospitalization was not considered to be indicated. In the spring of 1951 she had another attack of severe paralysis involving both upper limbs and preceded by pain. She was admitted to the Neurological Clinic of Serafimerlasarettet, where she remained for one week. Examination disclosed, in addition to the paralysis, diminution of the muscle reflexes. The cerebrospinal fluid was not examined nor was the serum potassium concentration determined. A roentgenogram of the cervical spine revealed slight thinning of the C₄-C₅ and C₅-C₆ intervertebral discs, but only slight degenerative reaction in the neighbouring tissues. The injection of prostigmine had no effect on the paralysis.—Since this attack the patient had occasionally been troubled by weakness and awkwardness of the hands and arms which, however, had each time spontaneously subsided within a few days.

In November 1953 she was readmitted to the Neurological Clinic with paralysis which had started a couple of days earlier in the hands and rapidly spread to the whole of the upper limbs and then to the lower limbs. Examination revealed almost total paralysis of all the limb muscles; she was only just able to move the toes and had very weak function in the flexors of the fingers and wrists. The muscles of the shoulder and neck were also involved, and there was distinct weakness of the jaws, with dysarthria and mild dysphagia. The limb muscle reflexes were abolished. She had no pain and sensation was normal. Blood potassium determinations (flame photometrical method) were made every day during the first week. The values were persistently subnormal and ranged from 5 to 7 mg. per cent. Other blood chemical determinations made included CO₂, NaHCO₃, phosphatase, and total proteins; all were normal. During the first few days the electrocardiogram showed major changes in the S-T segments and T wave, of the type found in hypopotassemia. Two days later oral administration of potassium citrate was instituted. Two days later a rapid improvement set in, and in less than a fortnight after the onset recovery was complete. The changes in the electrocardiogram also disappeared during this period. It was obvious that the improvement in the clinical condition commenced long before the serum potassium level returned to normal.

Electromyographic examinations of the patient were performed during the attacks of paralysis in both 1951 and 1953. On the latter occasion the electromyographic changes could be correlated to the serum potassium levels. The first recordings were made at the peak of paralysis and before potassium therapy was instituted. They showed, like those in 1951, a typical picture of myopathy, such as described in primary muscular diseases: muscular dystrophy, myotonic dystrophy and myasthenia gravis (Kugelberg, 1947, 1948, 1953), and also in myositis (Lambert *et al.*, 1950, Pinelli and Buchthal, 1951, Richardson,

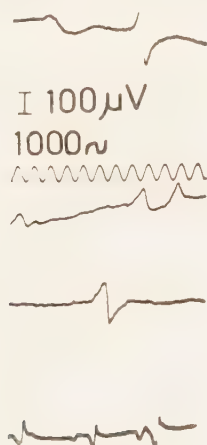


Fig. 1.

The electromyogram recorded from the biceps brachii muscle at the peak of paralysis in a case of periodic paroxysmal paralysis. Calibration, 100 microvolts. Time, 1000 cycles/second.

1951, Buchthal and Pinelli, 1952) as well as in some cases of rheumatoid arthritis, Petersén, 1954). Thus, on voluntary contraction of the muscle, the number of potentials recorded was very large in spite of the muscular weakness. The duration of the first three to four potentials recorded in each needle position was determined. Potentials led off from e.g. the biceps brachii and the extensors of the forearm were found to be very short, 1–3 m/sec. (Fig. 1), thus considerably shorter than in normal muscle (Jasper and Ballem, 1949; Petersén and Kugelberg, 1949). Numerous polyphasic forms were also observed. In our case, in contrast to cases of advanced muscular dystrophy, there was scarcely any area of muscle that was completely silent. On the other hand, in many needle positions electrical activity of a non-characteristic appearance was obtained, as is often the case when the needle point is placed at a distance from an active unit. A slight shift in the needle position, however, caused this activity to break up into distinct spikes.

the great majority of which were of the shape and duration shown in fig. 1. Spontaneous fibrillation potentials and abnormal insertion potentials were not observed.

Repeated electromyographic examinations in the next few days still showed a large number of action potentials in relation to the degree of paresis, but the mean duration of the potentials increased progressively as the clinical condition improved. On her discharge, at which time the paralysis had completely disappeared, the electromyogram was also normal. The serum potassium level, however, was still subnormal.

DISCUSSION

The clinical symptoms in this case were fairly characteristic of periodic paralysis. The age at onset, however, was remarkably high; the patient was over 60 at the inception of the disease. A high age of onset has, however, been reported by other authors (*Shinosaki*, 1925; *Berlin*, 1946; and others). In view of the intensity and wide distribution of the paralysis, the attack must be considered to have been severe; at the peak of the attack there was complete paralysis of the limb muscles with the exception of the most distal ones; according to earlier observers, the fingers and toes are rarely completely paralysed. Involvement of the muscles innervated by the cranial nerves is considered to be extremely uncommon, but in our case the attacks were associated with mild dysphagia, difficulty in articulation with slurred speech, and difficulty in chewing. The respiratory muscles were also slightly weakened, rendering coughing difficult.

Untreated attacks usually last from a few hours to three or four days. In our case the attack was of remarkably long duration, despite the administration of potassium; one week after the onset some weakness was still present in the affected muscles, especially those of the legs, where the muscle reflexes were still absent. *Jantz* states that the oral administration of a large dose of potassium chloride (15–20 gm.) will terminate an attack within one or two hours, but that smaller doses (2–3 gm.) have no effect. It is probable that in our patient the initial doses were inadequate. Two days after admission—four days after the onset—she received 5 gm. potassium by mouth, and the following day a further 5 gm. The drug was then withheld for 48 hours, after which she was given 15 gm. A considerable improvement was observed in her condition already after the first two doses.

Jantz's investigations point to complete parallelism between the clinical symptoms and the serum potassium levels, the latter returning

to normal simultaneously with diminution of the paralysis. On the other hand, he found that the electromyographic changes, studied by a method entirely different from that employed here, persisted after the other symptoms had subsided. In our patient disappearance of the electromyographic changes was concomitant with return of muscular power. The serum potassium concentration, on the other hand, was still as low as 7.2 mg. per cent a week after the onset, despite considerable improvement in the clinical symptoms. At that time the electromyogram was normal, and muscular power in the upper limbs was good. There was also good recovery of function in the lower limbs, although power against resistance was decreased. No further serum potassium determinations were made.

Our experiences in this case permit us to conclude, therefore, that a low concentration of serum potassium *per se* does not produce paralysis. This accords with the observations of earlier authors (*Gammon* and co-workers; *Tyler* and co-workers, 1951; and others). We also had the opportunity of examining two patients with potassium deficiency who, despite abnormally low serum potassium values, exhibited no paralysis and had normal electromyograms.

The electromyographic picture in our case exhibited changes in motor unit activity of the type shown to be characteristic of primary muscular diseases (*Kugelberg*, 1947). This is of interest in view of the general question whether periodic paralysis is nervous in origin or whether it is essentially a disorder of muscle function. Also worthy of note is the reported occurrence of muscular dystrophy in relatives of patients with periodic paralysis, which suggests that the two diseases may be remotely related (*Brain*, 1951). The electromyographic changes characteristic of myopathy and periodic paralysis include a decrease in the average duration of the action potentials and an increased number of potentials with a duration of 1–3 msec. *Kugelberg* ascribes the occurrence of these attenuated potentials to a gradual decrease in the number of fibres forming a motor unit. Another characteristic feature is the increased proportion of polyphasic action potentials. According to *Kugelberg*, these wave forms are the result of the muscle fibres of a unit being put out of action in an irregular way, and a consequent split-up of the motor unit potential. In muscular dystrophy this is generally caused by anatomical changes, though functional disintegration of the motor unit may also occur, manifested by the occasional elimination of one component in a polyphasic complex. It seems reasonable, therefore, to ascribe the electromyographic changes in periodic paralysis to a similar process: the attenuated potentials to a block in neuromuscular transmission, causing a large number of

the muscle fibres in a motor unit to fall out, and the polyphasic potentials to partial block. It is tempting also to assume that the lowered concentration of extracellular potassium would play a determining role by depriving the end plate regions of the potassium ions that are important to transmission. However, it is possible, as pointed out by *Jantz*, that the metabolic changes are far more profound and affect the phosphocreatine metabolism of the muscle fibres, in which case it might be possible that the motor end plate region is not the sole point of attack. Further support for the theory of disturbances of transmission as a cause of the functional disintegration of the motor unit activity in primary muscular diseases is the observation by *Lambert et al.* (1950) that electromyographic changes identical with those in these diseases can be produced in a normal muscle by intramuscular injection of curare.

The electromyographic studies of *Eichler* and co-workers (1940) in cases of periodic paralysis, with a technique quite different to the one employed in this study, showed during attacks an increase in the duration of the action potentials evoked by indirect electrical stimulation. The action potentials were led off from the surface of the skin, and consequently represent the summation of all electrical phenomena in the contracting muscle. These workers interpreted the increase in duration as a sign of delayed propagation of impulses through the muscle fibres, and draw an analogy with the prolonged Q-T interval often found in the electrocardiogram of patients with periodic paralysis. Thus, they came to the same conclusion regarding the pathogenesis of the electromyographic changes with their method as did *Kugelberg* (1947) and *Lambert* and co-workers (1950) from recording the motor unit activity.

SUMMARY

An electromyographic analysis of the motor unit activity in a case of non-familial periodic paralysis was made during and after an attack. At the time of paralysis electromyographic changes were demonstrated with a large number of action potentials in relation to the degree of paralysis, the majority of which were of considerably shorter duration than normal (1-3 msec.), as well as an increased proportion of polyphasic action potentials. The changes subsided parallel with retrogression of the clinical symptoms at a time when the serum potassium values were still considerably below normal. The findings are discussed and it is pointed out that the electromyographic picture is of the type found in primary muscular diseases.

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THE CELLULAR DENSITY IN GLIOMAS OF THE BRAIN

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The numbers of the constituent cells seen in a microscopic sight-field differ, widely or narrowly, from each other according to the different types of gliomas of the brain. Regarding this cellularity only vague descriptions have hitherto been recorded. In the case of medulloblastomas and oligodendrogliomas, for instance, *Bailey* (2) and *Hassin* (7) stated that they were "very cellular" tumors. "Richness in cells" was applied to glioblastoma multiforme (multicellular type) by *Busch* and *Christensen* (6). *Bailey* and *Cushing* (3) said that in astroblastoma "the structure of the tumor is loose." Astrocytomas were considered "relatively acellular" by *Bucy* and *Gustafson* (5). In a paper published by *Mabon*, *Spier*, *Adson* and *Kernohan* (9) it was stated with reference to astrocytoma grade 3 that "cellularity is greater." In a monograph of *Levin* (8) transitional gliomas were thought to be "ordinarily more than moderately cellular."

It is quite obvious that with such metaphysical expressions as those cited above, one is apt to be very confused when one wishes to figure out more exactly the nature of the cellularity in different types of gliomas of the brain. This is, in particular, true of students. And even among those who have had much experience in examining microscopic specimens of gliomas subjective discrepancies may readily ensue on judging the cellularity in any given glioma-preparation. Furthermore, difficulty may be encountered in determining how great quantitative difference in the cellularities should exist between astrocytomas, grades 2-3, and glioblastomas. The same holds true in differentiating transitional gliomas and glioblastomas by means of the cellularity.

In an extensive discussion of glioblastoma protoplasmicum, *Bergstrand* (4) stated as follows: "Die Zellen sind hier indes zahlreicher, wie aus den dichtliegenden Kernen zu ersehen ist," a statement in which the cellularity seems to be more clearly outlined as compared

with the descriptions mentioned above, but this is not concrete enough and of no practical importance.

Alexander (1), for the pathological diagnosis of primary intracranial neoplasms, advised using six differential characteristics; the first being the cellular density, by which he divided all the intracranial neoplasms into three distinct groups, namely, (a) *very cellular* with no or almost no stroma (Spongioblastoma multiforme, Medulloblastoma and Oligodendroglioma), (b) *markedly cellular* with some differentiation of stroma (Astroblastoma, Ependymoma, Polar Spongioblastoma, Pinealoma, etc.), and (c) *moderately cellular* with a great deal of stroma (Astrocytoma, etc.).

Although the scientific validity of *Alexander's* principle is beyond doubt, it is practically never easy to ascertain to what extent the tissue of an intracranial tumor under microscopic examination should be called "*very*," "*markedly*," or "*moderately cellular*."

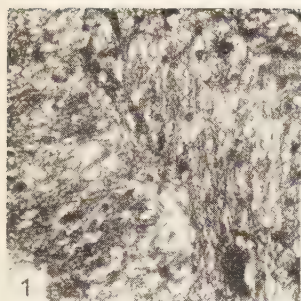
It seems, therefore, advisable numerically to standardize the descriptions concerning the cellularity (cellular density) in order that as little subjective discrepancy as possible should occur between the examiners who are to be confronted with one and the same histopathological specimen.

Since June 1951, I have fortunately had the privilege of attending the 1st Surgical Division (Prof. Dr. C. Araki), Kyoto University Medical School, Japan, for a histopathological study of the glioma group. During the study the view has arisen that, according to the different types of gliomas of the brain, the cellular density may differ, which can perhaps be indicated quantitatively, or numerically. Accordingly, the cellular density, the definition of which will be described below, has been determined in a total of 57 cases in *Araki's* series. Another 17 cases, sampled at random out of *Busch's* series, the microscopic preparations of which were obtained while I was working at the Neurosurgical Clinic (Prof. Dr. E. Busch) and at the Neuropathological Department (Dr. med. E. Christensen), Rigshospitalet, Copenhagen, during the period 1918-1950, have been examined in the same way for cellular density.

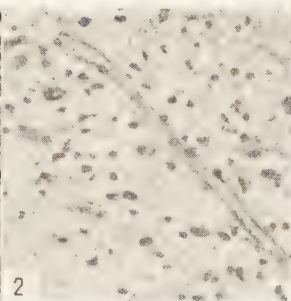
DEFINITION AND METHOD OF DETERMINATION OF THE CELLULAR DENSITY

The sections are made 4 to 6 microns thick. All kinds of staining methods which demonstrate both the nuclei and the cellular boundaries are available.

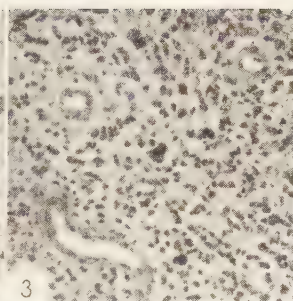
The number of the cells which constitute the tumor (glioma),



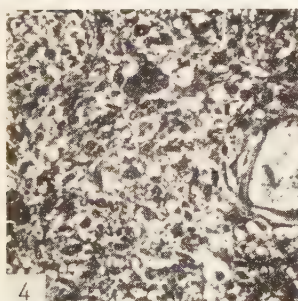
RS., $\times 450$.
Astrocytoma fibrillare.



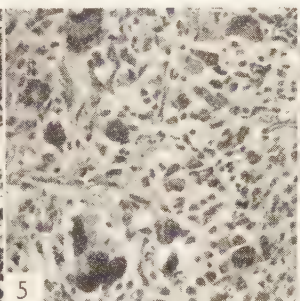
HE., $\times 300$.
Astrocytoma
protoplasmicum.



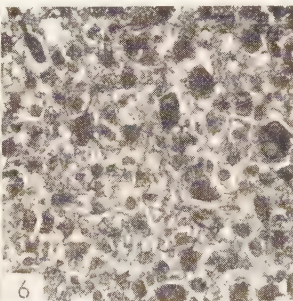
HE., $\times 200$.
Transitional Glioma.



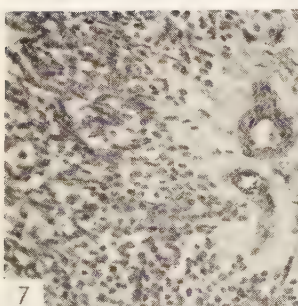
RS., $\times 450$.
Glioblastoma
multiforme.



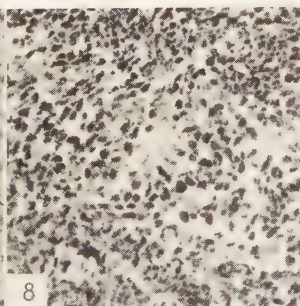
HE., $\times 450$.
Glioblastoma
multiforme.



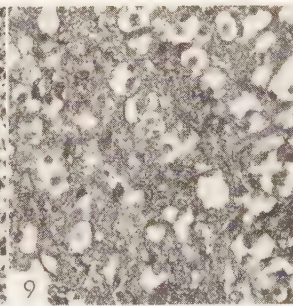
PTAH., $\times 450$.
Gemistocytoma.



HE., $\times 280$.
Ependymoma (cellular).



RS., $\times 450$.
Medulloblastoma.



RS., $\times 450$.
Oligodendroglioma.

counted in a microscopical sight-field under a magnification of $\times 600$, indicates the cellular density of the tumor in that sight-field.

Naturally, the number of cells is more easily and accurately counted, when the specimen is examined under high magnification with the use of oil-immersion. In this case, however, the distinction will often be so inconveniently feeble between the cellular and the rather acellular tumor, e.g. between a glioblastoma and a astrocytoma, that the difference between the cell numbers sometimes may not be significantly great. Under a magnification of lower than $\times 400$, cases inevitably occur in which the cell number seen in one sight-field is too great to be counted precisely.

At the selection of the fields to be examined, necrotic foci, blood vessels, hemorrhages, damages or defects of the tissue, and other degenerative changes are avoided as far as possible, since their presence will have a considerable influence on or reduce the value of the cellular density.

Thus, the cellular density is determined in at least five fields in each glioma specimen and the average cell number is accepted for the cellular density¹ of the glioma in question.

EXPLANATION OF THE TABLE

The following Table shows the results thus calculated in different gliomas of the brain, 74 cases in all. In *Araki's* series, the name of the patients, and in *Busch's* series, the number of the journals are entered.

Cases 17 and 18 in the column "Astrocytoma" are separately treated as belonging to the "t"-group. Consequently, the mean and the confidence interval of the cellular density in the astrocytomas are calculated in the sixteen cases numbered from 1 to 16. The reason for the exclusion from the group of "astrocytomas" of Cases 17 and 18 will be discussed later together with the "t"-group in the column "Glioblastoma."

Cases 6, 7, and 8 were largely gemistocytomas, astroblastomas, and polar spongioblastomas, respectively, but some of them were confirmed histopathologically to be astrocytomatous.

Case 13 received two operations: the specimen from the 1st operation proved to be preponderantly astrocytomatous and the tumor tissue

¹ Strictly speaking, as regards the cellular density, the average space of the constituent cells must be taken into consideration concurrently with the mean number of the cells. It is, however, practically impossible to measure with accuracy the space taken up by each cell, since the cells are usually very irregularly shaped and their protoplasmic processes are wavy, intercrossing, entangled and/or gradually tapering off.

Astrocytoma		Araki		Busch		Tumors		Penckhaus		G. and H. G. and H.		droghda	
1	S. O. ¹	180	$\left\{ \begin{array}{l} \text{M. W.} \\ \text{K. N.} \\ \text{K. H.} \\ \text{J. M.}^4 \\ \text{K. L.} \\ \text{H. T.} \\ \text{A. I.} \\ \text{T. H.} \end{array} \right\}$ $\left\{ \begin{array}{l} \text{K. T.} \\ \text{S. S.}^5 \\ \text{K. H.} \\ \text{S. H.} \end{array} \right\}$ $\left\{ \begin{array}{l} \text{K. M.}^3 \\ \text{I. F.} \\ \text{T. N.} \end{array} \right\}$ $\left\{ \begin{array}{l} \text{T. N.} \\ \text{E. H.} \end{array} \right\}$	$\left\{ \begin{array}{l} 355 \\ 341 \\ 492 \\ 350 \\ 418 \\ 319 \\ 371 \\ 418 \end{array} \right\}$ $\left\{ \begin{array}{l} 408 \\ 216 \\ 210 \\ 254 \\ 280 \\ 294 \\ 288 \end{array} \right\}$ $\left\{ \begin{array}{l} 270 \\ 241 \\ 210 \\ 254 \\ 280 \\ 294 \\ 288 \end{array} \right\}$	$\left\{ \begin{array}{l} 04530 \\ 03284 \\ 03280 \\ 03065 \\ 03115 \\ 03307 \\ 04092 \\ 01997 \end{array} \right\}$ $\left\{ \begin{array}{l} 411 \\ 474 \\ 489 \\ 550 \\ 422 \\ 405 \\ 453 \\ 288 \end{array} \right\}$ $\left\{ \begin{array}{l} 283 \\ 256 \\ 147 \\ 292 \\ 244 \\ 265 \\ 472 \\ 421 \end{array} \right\}$ $\left\{ \begin{array}{l} \text{K. N.} \\ \text{M. H.} \\ \text{M. H.} \\ \text{T. Y.} \\ \text{K. H.} \\ \text{N. S.} \\ \text{N. S.} \\ \text{K. H.}^7 \end{array} \right\}$ $\left\{ \begin{array}{l} \text{Y. K.} \\ \text{Y. K.} \\ 03808 \\ 04882 \end{array} \right\}$ $\left\{ \begin{array}{l} 294 \\ 280 \\ 329 \\ 347 \\ 242 \\ 346 \\ 218 \end{array} \right\}$ $\left\{ \begin{array}{l} 702 \\ 676 \\ 690 \\ 614 \\ 736 \\ 639 \end{array} \right\}$	$\left\{ \begin{array}{l} \text{Y. K.} \\ \text{S. N.} \\ \text{K. K.} \\ \text{S. T.} \\ \text{K. L.} \\ \text{Pbl.} \end{array} \right\}$ $\left\{ \begin{array}{l} 294 \\ 280 \\ 329 \\ 347 \\ 242 \\ 346 \\ 218 \end{array} \right\}$ $\left\{ \begin{array}{l} 702 \\ 676 \\ 690 \\ 614 \\ 736 \\ 639 \end{array} \right\}$	$\left\{ \begin{array}{l} \text{A. M.}^9 \\ \text{Y. K.} \\ 03041 \\ 03633 \end{array} \right\}$ $\left\{ \begin{array}{l} 248 \\ 314 \\ 279 \\ 346 \end{array} \right\}$						
2	K. A.	165											
3	I. K.	192											
4	H. K.	104											
5	K. K.	163											
6	S. N.	120	$\left\{ \begin{array}{l} \text{S. T.} \\ \text{T. N.} \end{array} \right\}$	$\left\{ \begin{array}{l} 242 \\ 346 \\ 218 \end{array} \right\}$	$\left\{ \begin{array}{l} 736 \\ 639 \end{array} \right\}$	$\left\{ \begin{array}{l} 03492 \\ 03894 \end{array} \right\}$	$\left\{ \begin{array}{l} 361 \\ 361 \end{array} \right\}$	$\left\{ \begin{array}{l} 297 \\ 297 \end{array} \right\}$					
7	K. N.	144											
8	A. N.	141											
9	T. U.	128											
10	Y. O.	145											
11	S. N.	144											
12	K. I.	139											
13	K. M. ²	166											
14	03744	158											
15	03108	172											
16	03560	169											
17	t	S. T.	242										
18		T. N.	267										

$\frac{1}{N} \sum_{i=1}^N x_i = 152$	$\frac{1}{N} \sum_{i=1}^N x_i = 275$	$\frac{1}{N} \sum_{i=1}^N x_i = 271$	$\frac{1}{N} \sum_{i=1}^N x_i = 408$	$\frac{1}{N} \sum_{i=1}^N x_i = 458$	$\frac{1}{N} \sum_{i=1}^N x_i = 394$	$\frac{1}{N} \sum_{i=1}^N x_i = 298$	$\frac{1}{N} \sum_{i=1}^N x_i = 676$	$\frac{1}{N} \sum_{i=1}^N x_i = 297$
164 ~ m	140	291 ~ m ₁	464 ~ m ₂	503 ~ m ₃	460 ~ m ₄	354 ~ m ₅	724 ~ m	361 ~ m

Table: The Cellular Density in Gliomas of the Brain.

Counting fractions of 0.5 and over as a whole number and disregarding the rest.

Taking 0.05 as the level of significance, the confidence intervals are calculated from the following statistical formula:

$$\frac{1}{x} \pm \frac{N}{N-1} \sum_{i=1}^N x_i^2 \pm \frac{1}{N-1} \sum_{i=1}^N (x_i - \bar{x})^2 \pm \frac{1}{N-1} \sum_{i=1}^N x_i^2$$
$$F \geq \frac{N(\bar{x} - m)^2}{u^2}, \text{ deg. of fr.: } \begin{matrix} n = 1 \\ n = N-1 \end{matrix}$$

The small numerals correspond to the number in the figures inserted at the end of this paper.

Table: The Cellular Density in Gliomas of the Brain.

Counting fractions of 0.5 and over as a whole number and disregarding the rest.

Taking 0.05 as the level of significance, the confidence intervals are calculated from the following statistical formula:

$$\bar{x} = \frac{1}{N} \sum_{i=1}^N x_i, u^2 = \frac{1}{N-1} \sum_{i=1}^N (x_i - \bar{x})^2 = \frac{1}{N-1} \left\{ \sum_{i=1}^N x_i^2 - N \bar{x}^2 \right\}$$

$$F \geq \frac{N}{u^2} \left(\frac{\bar{x} - m}{N-1} \right)^2, \text{ deg. of fr. } \begin{matrix} n = 1 \\ n = N-1 \end{matrix}$$

The small numerals correspond to the number in the figures inserted at the end of this paper.

removed at the 2nd operation, for recurrent symptoms, showed some malignancy in the cell differentiation.

In the group "b," in the column "Glioblastoma," Cases 9 and 10 contained a great number of multinucleated ring cells, on an average more than ten in one field. In Cases 11 and 12, the tissues predominantly consisted of large gemistocytes and/or of large cells with lobulated nuclei. In short, the cases included in the "b"-group were all of the magnocellular type (*Busch Christensen*) of glioblastomas. On this account, the cellular density in these four cases was thought to be significantly less in number than that of the "a"-group. This held true in the "b"-group, too, for the tumor tissue was characterized by interposition of multiple and widespread angionecrotic foci in nearly all the sight-fields (Case 01997).

In the column Ependymo-chorioid Tumors, Case 1 was a chorioid plexus papilloma; Cases 2 and 6 were papillary ependymomas; Case 3 was the myxopapillary part of Case 2; Cases 4 and 5 were epithelial ependymomas, and the Cases from 7 (identical with Case 6) to 11 were cellular ependymomas. Since there is an extreme diversity in the structural arrangements, and in the cellular morphology as well, according to different types of the ependymoma group, the cellular densities are also very variable. Hence, the cellular density was calculated only in the cellular type as grouped in "c."

In the column Pinealoma and Pineoblastoma, the former (Cases 1-5) was only taken into consideration for statistical purposes and the latter ("Pbl.") was disregarded. It may be said in this connection that the cellular density in this group is a sum of the numbers of both parenchymatous cells and lymphoid cells. However, the fields were selected so that they contained the fewest lymphoid cells.

COMMENT

The means and the confidence intervals (C.I.) of the cellular density in different types of the gliomas are shown in the following:

	Mean	C.I.
Astrocytoma	152	$164 \geq m \geq 140$
Gemistocytoma	266	
Astroblastoma	240	
Spongioblastoma polare	214	
Glioblastoma {Araki	408	$464 \geq m_a \geq 352$
{Busch	458	$503 \geq m_{a'} \geq 413$
Ependymoma (cellular)	394	$460 \geq m_c \geq 329$
Pinealoma	298	$354 \geq m_p \geq 242$
Medulloblastoma	676	$724 \geq m \geq 628$
Oligodendroglioma	297	$361 \geq m \geq 233$

From the result of the statistical calculations listed above, it will be understood that the cellular density around 150 (astrocytoma) corresponds with the term "relatively acellular" suggested by *Bucy* and *Gustafson* (5), or with that ("moderately cellular") given by *Alexander* (1).

Provided that the cellular density over 400, between 200 and 400, and less than 200 be called "very cellular," "moderately cellular," and "relatively acellular," respectively, astrocytomas are, in fact, "relatively acellular" tumors, and glioblastomas and medulloblastomas in particular are "very cellular" tumors. The remaining types of gliomas are to be considered as "moderately cellular."

Oligodendroglioma, which has been thought to be a very cellular tumor, is in reality a glioma of moderate cellularity. The misconception as yet harboured that oligodendrogliomas are very cellular tumors seems undoubtedly due to the fact that in the oligodendroglioma the constituent cells appear so densely packed together. But, on the base of the statistical result listed above, it may be assumed that the clear haloes surrounding the nuclei of the cells occupy a surprisingly great space.

"t"-Group:

Cases 17 and 18 in the column "Astrocytoma," were, as stated above, separately treated, since they were rather atypical of an astrocytoma. They contained multinucleated giant cells and/or even mitotic figures, on an average 1 to 2 in every other sight-field. Besides, there were occasionally vessels with a hypertrophied wall. However, polymorphism of cells was not quite striking and the tissue was rather avascular.

The "t"-group in the column "Glioblastoma," comprising five cases (13-17), may perhaps be classified as "Glioblastoma" in a wide sense. However, multiformity of cells and multifarious aspects of the tissue as a whole were not so conspicuous as in the cases included in the groups "a" and "b." Moreover, in these five cases, the tumors were macroscopically confirmed to be located subcortically with a clear demarcation from healthy parts of the brain substance, and to have a cyst, or cysts, containing xanthochronic clear fluid.

In short, the cases, totalling seven, included in the "t"-groups were either astrocytomas, grades 3-4 (the Mayo Clinic), the intermediate type of Ringertz, or the so-called transitional gliomas of the Globus school.

The cellular densities in the "t"-Group ranged from 242 to 294; the mean and the confidence interval being 275 and 291-271, respectively.

That is to say that the so-called transitional gliomas are, as regards cellular density, also intermediary between the relatively acellular astrocytomas and the very cellular glioblastomas.

It may happen that one comes upon some suspected astrocytomas which possess rather many undifferentiated cells, giant cells, and even mitotic figures, but one is still hesitant whether to classify the tumors in question in the category of astrocytoma or in that of glioblastoma. This is true of atypical or suspicious glioblastomas and of questionable transitional gliomas, since in biological material there is generally some overlapping of groups and of characteristics. In such cases, however, the cellular density would, in the author's opinion, be a convenient criterion; when the cellular density is over 400, the tumor should preferably be classified as a glioblastoma; if between 200 and 400, as a transitional glioma, and when less than 200, as an astrocytoma.

If the cellular density only is taken into consideration, the gemistocytoma, the astroblastoma, and the polar spongioblastoma may likewise be ranged in the group of "Transitional Gliomas."

SUMMARY

The cellular density (the number of the cells counted in a microscopical sight-field under a magnification of $\times 600$) was calculated in different gliomas of the brain, comprising 74 cases.

The means and the confidence intervals of the cellular density were as follows: Astrocytoma 152 (164-140), Glioblastoma 408 (464-352) in *Araki's* series and 458 (503-413) in *Busch's* series, Ependymoma (cellular) 394 (450-329), Pinealoma 298 (345-242), Medulloblastoma 676 (724-628), and Oligodendroglioma 297 (361-233).

Provided that the cellular density of over 400, between 200 and 400, and less than 200 be defined as "very cellular," "moderately cellular," and "relatively acellular," respectively, it can be said that glioblastomas and medulloblastomas are "very cellular" tumors, and astrocytomas are "relatively acellular" tumors. Gliomas other than these three types should be considered "moderately cellular" tumors, to which oligodendrogliomas also belong.

As regards cellular density, the so-called transitional glioma also ranks between the "relatively acellular" astrocytoma and the "very cellular" glioblastoma.

When the cellular density only is taken into consideration, gemistocytomas, astroblastomas and polar spongioblastomas may likewise be classified as transitional gliomas.

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AN ANALYSIS OF CAUSES OF POSTOPERATIVE LIMB PARESES FOLLOWING ANTEROLATERAL CHORDOTOMY

By

C. G. BERNHARD, E. BOHM and I. PETERSÉN

INTRODUCTION

Anterolateral chordotomy has been frequently employed to free the patient from severe and intractable pain caused, as a rule, by malignant growths within the region of the spinal nerve root innervation. A not infrequent complication of anterolateral chordotomy is a postoperative paresis of the extremities.

Peet (1926) reported a series of 19 patients undergoing surgery, of which 6 resulted in a flaccid paraparesis following bilateral chordotomy. In a series of 4 unilateral and 8 bilateral chordotomies (*Stör* 1931), 5 instances of flaccid paresis resulted from bilateral intervention, involving one extremity in 2 cases and both extremities in 3. For the most part the pareses were reversible. The unilateral chordotomy was complicated in one instance by a paresis of one extremity. *Babitchine* (1936) reported that paresis was encountered in 35 % of his series of 34 chordotomies following, for the most part, a bilateral procedure. The motor weakness was transitory and function returned completely or partially in 4–6 weeks. *Petit-Dutaillis* (1938) found that motor weakness resulted in 6 of the 29 chordotomies, appearing only in the bilaterally operated patient. In a series of 54 bilateral and 55 unilateral thoracic chordotomies (*Grant* 1941), postoperative paresis appeared in 17 % and 6 % of the cases, respectively. *White et al.* (1950) assert that this complication appeared in 4 % of unilateral chordotomy (126 cases) and twice as often in bilateral chordotomy (84 cases). The last two authors do not state whether the pareses are of a flaccid or spastic character.

It would appear that postoperative paresis rather often results from anterolateral chordotomy and the prospect of this complication can,

at times, constitute a serious contraindication to surgery. Different opinions are offered as to the causes of this postoperative weakness. Accordingly, in an effort to ascertain the causes of postoperative paresis, the present authors have undertaken this study of chordotomized patients and collated their findings with those derived from experimental investigations on monkeys.

CLINICAL SECTION

The cause of postoperative paresis has been attributed by many authors to a direct or indirect injury to the lateral pyramidal tract during surgery. This tract, according to *Suh and Alexander* (1939), is supplied by branches from the anterior spinal artery which pass through the anterolateral quadrant. *White et al.* (1950) assert that paresis can result from a lesion of one of these branches, which produces a necrosis of the lateral pyramidal tract. They further assert that when the most ventral portion of the pyramidal tract is injured by the chordotomy incision, a paresis does not ensue. This conclusion was also reached by *Hyndman* (1941), who called attention to the fact that 3 of his chordotomy cases which were subjected to postmortem examination showed evidence of lateral pyramidal tract damage although clinically such injury was undetectable. *Kahn and Rand* (1952) affirm that the postoperative paresis depends on a direct injury to the lateral pyramidal tract through the incision itself. The denticulate ligament can be stretched through rotation of the spinal column and, as a consequence, orientation becomes difficult and the incision is made too dorsal. *Grant* (1941) also has an impression that postoperative paresis results from a direct injury to the lateral pyramidal tract.

Putnam's (1940) method of treatment of paralysis agitans by the section of the lateral pyramidal tract has shed new light on the significance of this tract for motor activity. The postoperative paresis which is noted in these cases has as a rule been of a minor degree and in most instances to a large extent characterized by a subsequent return of function (*Putnam and Herz* 1950). *Oliver* (1953) likewise asserts that in a number of his cases operated on by this method, no motor deficits resulted.

The methods of *Ebin* (1949) employed for this condition, in which both the lateral and the contralateral ventral pyramidal tracts are sectioned, is not accompanied by a complete paralysis but only by a diminution of approximately 60 % of motor activity. The pathogenesis of the gross paresis following the use of this method will be discussed below.

Hyndman (1941) has studied the motor effect of a total section of the complete anterior portion of the spinal column. He found that in the case of bilateral chordotomy which included the anterior column, a flaccid paraparesis appeared and remained a few days accompanied by a loss of extensor tonus of long duration. This is attributed by this author to the fact that the extrapyramidal tract in the forward portion of the spinal column "contributes to the sustained contraction of the antigravity muscles, such as is necessary in standing and walking. The loss of strength which follows anterior chordotomy is often a subjective complaint rather than an objective finding."

The surgical technique reported by *Oliver* (1953) for paralysis agitans further illuminates the motor functions associated with the anterior portion of the spinal column. By this method the incision of *Putnam* (1940) is extended to include the anterolateral column and results in an immediate hemiplegia which does not regress to the extent seen from section of only the lateral pyramidal tract.

As a result of the foregoing studies, different authors have reached various conclusions with regard to the cause of postoperative pareses following anterolateral chordotomy. For the most part, an injury to the lateral pyramidal tract is indicated, but some authors assert that a selective section of that tract produces only fleeting motor weakness and occasionally no weakness at all. On the other hand, a complete section of the anterior half of the spinal column produces a flaccid paresis as well as loss of extensor tonus which persists for a long time, while a combination of these incisions, *i.e.* section of the lateral pyramidal tract and the anterolateral column, produces a pronounced paresis which does not regress to the same degree as the paresis which appears following the section of only one tract.

MATERIAL

The clinical material included 29 unilateral and 31 bilateral chordotomies operated upon at the Neurosurgical Clinic of the Serafimer-lasarettet from 1931 to 1953. Seven cases have been excluded from the series either because records are not available as to whether motor changes persisted at the time of discharge, or because gross paresis present before operation complicated the postoperative evaluation of motor changes. Information of the patient's condition after discharge has been obtained from communication with the patient's subsequent physician and from annual correspondence with the patient.

Operation was performed with the usual technique under local anaesthesia. Incision in the spinal column began at the attachment

of the denticulate ligament and ended at the point of emergence of the anterior root. Then the degree of analgesia was tested and the incision enlarged, if necessary, in the medial-ventral direction with care being taken not to injure the dorso-lateral column.

16 of the *unilateral* chordotomies were carried out in the upper thoracic region and 13 at various levels of the cervical region. Most of these patients had disease processes of a benign nature (root pain, herpes zoster). In this series only one case of monoparesis was encountered, where chordotomy had been performed on a level with Th 3-4 for pain caused by arthrosis deformans coxae. A complete spastic paralysis

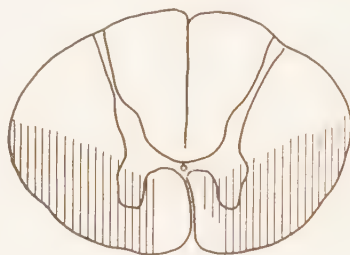


Fig. 1.

The shaded areas show the extent of the incisions in a case of bilateral chordotomy in the upper thoracic region. The operation was followed by a paraparesis.

appeared about 10 hours after surgery but regressed quickly, so that at the time of discharge one month after operation, the patient could walk relatively well. One year after surgery the patient reported that strength in the leg had returned.

The *bilateral* chordotomy series comprised 31 patients, 25 incisions being performed at the upper thoracic and 6 at various levels of the cervical region. As a rule these patients had some form of malignant process. Following the thoracic chordotomies, a paraparesis ensued in 13 cases and a monoparesis in 2. Following the cervical chordotomies a paraparesis was encountered in one case. These paraparesis were in 10 instances of a flaccid nature with loss of reflexia, while in the remaining 3 cases no information is available as to the nature of the paresis. In all instances the surgeon stated that incision was carried out with the technique described above and that the area of trans-section apparently was not larger than usual. The majority of the patients, as mentioned above, were operated upon for pain resulting from malignancy, and the postoperative period of observation was therefore rather short. Of the 13 postoperative pareses, 10 were associated with malignancy. During the time of observation the pareses had not shown evidence of regression, but the survival time was too

brief to permit a definite statement as to whether or not the motor weakness was reversible. On the other hand, in 3 cases paraparesis appeared in patients whose underlying illness was of a benign or a "semi-malignant" nature and here the period of observation was in 2 cases more than one year and in one case more than 4 years. The motor weakness was of a flaccid nature and showed no evidence of restitution of function and invalidated the patient to a greater or less extent.

Of the two cases of postoperative monoparesis, one was transitory and function returned within the course of 3 weeks. The other was

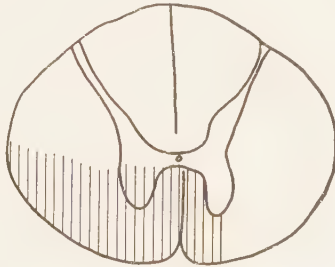


Fig. 2.

The shaded area shows the extent of the incision in a case of unilateral chordotomy in the mid-thoracic region. No paresis followed the operation. Note that the incision also involves the contralateral anterior column.

a flaccid paresis which appeared after surgery and was irreversible in the 2 years of follow-up. In the latter case the surgeon had an impression that the area of incision on the paretic side included the largest part of the ventral quadrant.

Lastly, the series contains two cases of postoperative areflexia of the lower extremities without any motor changes.

In this study, therefore, the frequency of postoperative paresis following bilateral chordotomy was about 50 % and motor changes have almost invariably appeared following the bilateral procedure.

A histological check of the limits of the incision in those instances of postoperative paresis which showed no evidence of regression was often difficult to obtain. The patient usually had been transferred to other institutions for further care and postmortem examination could not be arranged. Through the courtesy of the late Dr. O. Sjöqvist we have had access to the histological slides from two chordotomy patients who died one month after operation. In one case (Fig. 1) a bilateral chordotomy had been performed in the upper thoracic region. Postoperatively a flaccid paraparesis ensued and one month following surgery only an insignificant movement of the knee and ankle could

be elicited. Figure 1 shows that the largest portion of the anterior quadrants had been sectioned without involvement of the lateral pyramidal tracts.

In the other case a unilateral chordotomy had been performed in the upper thoracic region. Figure 2 reveals that the entire anterior quadrant had been sectioned and that at surgery a small lesion had unavoidably been induced in the anterior column of the contralateral side. No postoperative paresis appeared in this case.

EXPERIMENTAL SECTION

In view of the numerous investigations which have previously confirmed the importance of activity in the descending bulbospinal system within the anterior half of the spinal column for the spinal motor neuron excitability (see *Sherrington* and *Leslett* 1902, 1903, *Lloyd* 1941, *Magoun* and *Rhines* 1946, *Rhines* and *Magoun* 1946), it would appear that more consideration than was formerly accorded should be given the function of the anterolateral tracts in its significance for postoperative paresis following anterolateral chordotomy.

In earlier investigations on the spinal motor neuron activity following cortical stimulation in monkeys, the authors have shown that the response in the ventral root transmitted by the pyramidal tract after cortical electrical stimulation could not be elicited when the anterior half of the spinal column was sectioned leaving the lateral pyramidal tract completely intact (*Bernhard, Bohm* and *Petersén* 1953). The present investigations also indicate that the anterior half of the spinal column is of decisive importance for the motor activity relayed from the higher centres.

As a background to a discussion of complications of the anterolateral chordotomy we have, therefore, undertaken a series of investigations of the significance of the anterolateral tract for the activity in the ventral roots elicited by electrical stimulation of the motor region of the cortex.

METHOD

The experiments were carried out on monkeys (*Macaca Mulatta*) under light nembutal narcosis. A small dose of d-tubocurarine was given to prevent disturbing movements when the precentral region was stimulated. The head was fixed and the spinal column immobilized by a clip applied to the thoracic and sacral region. The skull was opened, covered with paraffin oil (38° C.), and the dura opened under paraffin. When the lumbosacral laminectomy had been completed, the spinal

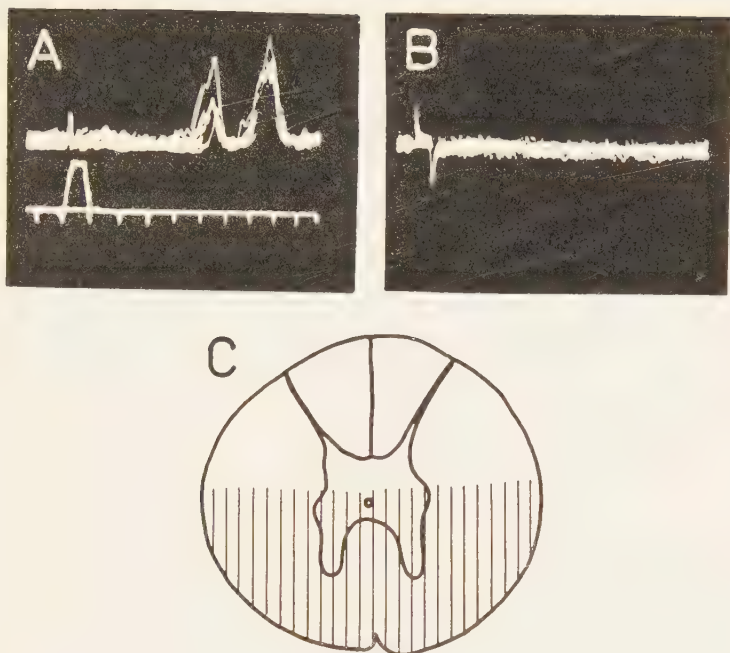


Fig. 3.

A, superimposed records of action potentials recorded from the L7 ventral root following repetitive stimulation of the contralateral precentral gyrus. Record B was taken after transection at cervical level of the anterior part of spinal cord.

The shaded area in C indicates the extent of the transection. Time in msec.

region was covered with warm liquid paraffin. Electrical square wave shocks (duration 0.2–1 msec.) were used for stimulation of the cortex. Action potentials were recorded from the ventral root and from the sciatic nerve. In a few experiments the action potentials were recorded also from the pyramidal tract by means of a needle electrode, the position of which was checked histologically.

RESULTS

Fig. 3 shows the result of an experiment in which the anterior portion of the spinal column was transected during the course of the experiment. The hind limb area within the precentral region was stimulated and the action potentials recorded from the contralateral L7 ventral root. Figure 3 A shows superimposed oscillograms of the action potentials in the ventral root following each stimulus in a train of shocks applied within the precentral gyrus. The stimulation frequency was 25 per sec. and the picture was taken two seconds after the be-

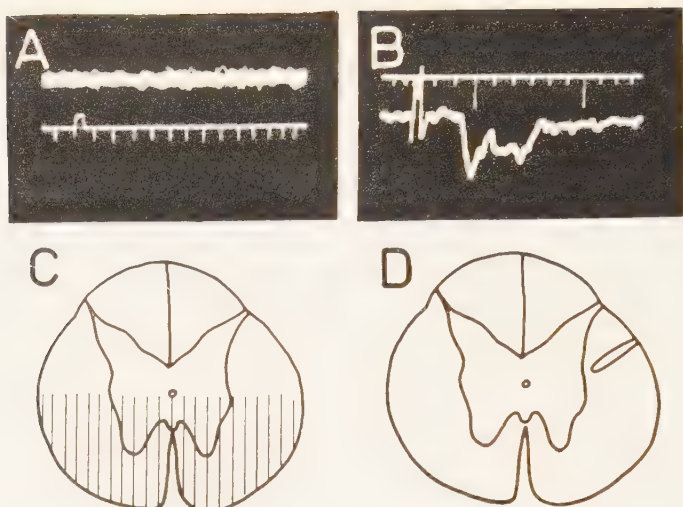


Fig. 4.

A, superimposed records obtained from the right sciatic nerve following repetitive stimulation of the contralateral precentral gyrus after partial spinal transection (shaded area in C). B, action potentials following stimulation of the contralateral precentral region recorded from the right lateral pyramidal tract below the incision marked in C. D shows the position of the recording needle-electrode in the lateral pyramidal tract. Time in msec. For further explanation see text.

gining of the repetitive stimulation. As can be seen, each stimulus is followed by a series of action potentials in the ventral root, the first wave in this instance having a latency of 4.5 msec. The first action potential has been shown to be monosynaptically transmitted from the pyramidal tract to the spinal motor neurons (*Bernhard, Bohm and Petersén 1953*). The first action potential is followed by a series of action potentials. These action potentials in the L 7 ventral root appear with great regularity in each stimulation series. The anterior portion of the spinal column was then sectioned with a tractotome in the upper cervical region. Fig. 3 C is a composite of a series of histological sections in this region and shows that the chordotomy only involves the anterior half of the spinal cord leaving both lateral pyramidal tracts intact. The cortex was stimulated again and it can be seen that the cortical stimulation was not followed by any response in the ventral root (Fig. 3 B).

We also conducted a series of investigations of a similar type, which differed only in that the chordotomy was performed 3–8 weeks before the electrophysiological study was performed. Fig. 4 shows the results of such a study. Fig. 4 C pictures the limits of the chordotomy by means of histological sections through the region where the chordo-

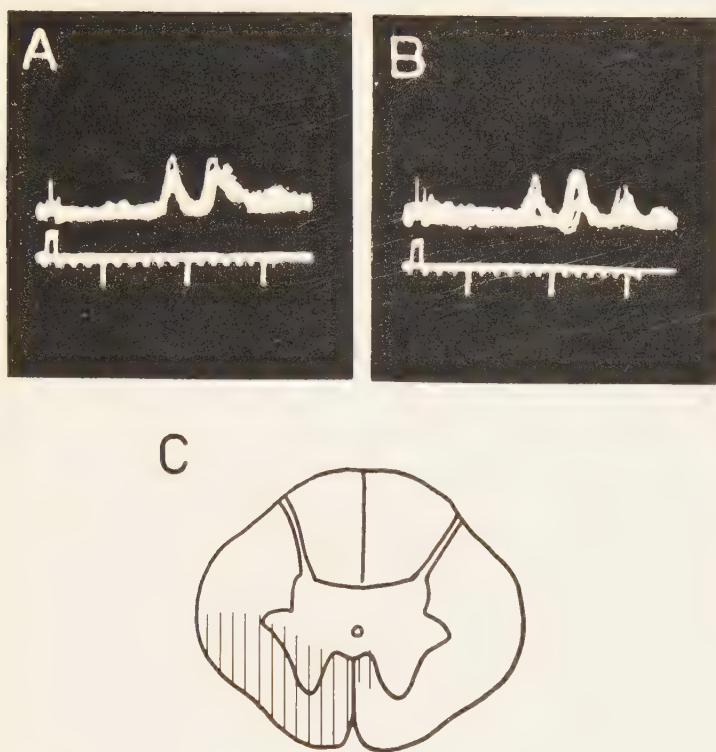


Fig. 5.

A and B, superimposed records of responses obtained from the right (A) and the left (B) sciatic nerves following contralateral stimulation of the precentral gyrus after partial spinal transection in the upper thoracic region (shaded area in C). Time in msec.

tomy was performed (upper thoracic region). Only the anterior portion of the spinal column was sectioned and the lateral pyramidal tract was left completely intact. Nor in this case could any response be obtained in the L7 ventral root upon stimulation of the contralateral precentral gyrus (Fig. 4 A). To demonstrate that impulses were transmitted from the cortex through the lateral pyramidal tract, a record was obtained by means of a needle electrode inserted in the lateral pyramidal tract immediately below the incision in the spinal cord, and on the same side as the root from which the tracing had been previously obtained. Fig. 4 D shows the histological check of the position of the needle electrode. The oscillogram in Fig. 4 B demonstrates that the cortical stimulation was followed by impulse responses in the lateral pyramidal tract.

Fig. 5 shows the results of an experiment on a monkey in which a

unilateral chordotomy had been performed 8 weeks earlier. The extent of the incision is shown in Fig. 5 C. Records A and B in Fig. 5 show the action potentials which were led off from the sciatic nerves following contralateral cortical stimulation. As can be seen, responses could be obtained from both nerves in spite of one of the anterior quadrants being destroyed by the incision. Note that the extent of the incision is similar to that in Fig. 2.

DISCUSSION

In our clinical material a temporary monoparesis appeared after unilateral chordotomy (29 cases) in only one instance. Moreover, the paresis appeared about 10 hours after operation and was of a spastic nature. It is therefore most probable that the cause of this paresis was a vascular change which led to edema or partial necrosis of the lateral pyramidal tract.

Among the 31 cases of bilateral chordotomy parapareses appeared in 13 cases, of which only 10 could be established as flaccid, which conforms to *Hyndman's* observations. Most of these patients were followed for only 3 months after surgery and during this time no significant restoration of function was noted. Unfortunately only 3 cases of postoperative pareses could be followed from 1 to 4 years and in these cases only partial restoration was noted, demonstrating that *after bilateral chordotomy a flaccid paresis of long duration may appear*.

As mentioned above, a number of earlier investigations have shown that the activity in descending tracts in the anterior region of the spinal column is of decisive importance for the excitability of the spinal motor neurons. This fact is clearly illustrated in our monkey experiments, in which the lumbar motor neurons could not be activated by cortical stimulation when the anterior part of the spinal cord was sectioned, despite the fact that the lateral pyramidal tracts were left intact and shown to conduct impulses from the stimulated cortex. By sectioning the anterior part of the cord the influence of the facilitatory bulbospinal system on the spinal motor neurons is eliminated. The facilitatory action of this system seems to be necessary for the activation of the spinal motor neurons by cortical stimulation of the cortico-spinal neurons which descend in the lateral pyramidal tracts (cf. *Bernhard, Bohm and Petersén 1953*).

We believe that the appearance of a flaccid paresis following bilateral chordotomy in humans depends on the question whether the incision affects the entire or the largest part of the anterior quadrants of the spinal cord either as a direct result of the incision itself or

indirectly through circulation changes resulting from the incision. This suggestion is confirmed partly by the electrophysiological investigations and partly by the case illustrated in Fig. 1. The investigations on monkeys show that the motor neuron activity in the lumbar region resulting from *electrical stimulation of the cortex* disappears when the anterior quadrants of the spinal cord are sectioned despite the fact that the function of the lateral pyramidal tracts is preserved. In *humans* a flaccid paresis may appear after an almost complete transection of the anterior quadrants with preservation of intact lateral pyramidal tracts, as illustrated by the case presented in Fig. 1 (cf. *Hyndman* 1941). The observations by *Stör* (1931) also support our conclusion. He found by histological examination of two cases complicated by postoperative paraparesis that the anterior half of the spinal column contained edema and was punctured by small hemorrhages. Neither hemorrhage, edema nor degenerative changes could be seen within the region of the lateral pyramidal tract.

If the pareses were due to a direct injury to the lateral pyramidal tracts brought about by the incision, then the bilateral chordotomy should produce *monoparesis* twice as frequently as the unilateral operation and not, as usually happens, almost solely paraparesis. Points of orientation on the spinal cord surface are so definite that it is improbable that the cause of the postoperative pareses should be due to an undesired transection of the largest part of the lateral pyramidal tract. The limits of the incision would then be just as large as or larger than those described by *Oliver* (1953) and *Ebin* (1949) for treatment of the Parkinson tremor, where, as was noted, a long-lasting spastic paresis results. That the method described by *Ebin* produces such a gross paresis is due to the fact that the incision involves not only the lateral and the contralateral ventral pyramidal tract, but also a large part of the anterior half of the spinal column, since his patients postoperatively showed a contralateral analgesia corresponding to the level of transection. Here, with great probability, a great part of the anterior quadrant was also transected.

In all published materials the frequency of postoperative paresis after unilateral chordotomy is significantly lower than after bilateral section. The reason for this, we believe, is that the descending facilitatory tracts in the anterior half of the spinal cord both decussate and run without decussation (*Rhines* and *Magoun* 1946) and, as a consequence, a paresis does not invariably result when the tract system of one side is interrupted (see Figs. 2 and 5).

The question is: can paresis be avoided in anterolateral chordotomy? In the overwhelming majority, bilateral transection is em-

ployed for intractable pain caused by a malignant tumor. Most of the pareses appear to be fleeting, but inasmuch as restoration can be delayed for several months, the patient, despite the disappearance of pain, has been deprived of part of the benefit of operation especially since the postoperative span of life for these patients is comparatively short. In those instances in which a lasting paresis is encountered in the patient operated upon for intractable pain of benign etiology, the patient is even "worse off".

Probably the facilitatory system has a more or less diffuse distribution within the anterior quadrants, and paresis will appear if a large portion of the anterior part of the spinal cord has been destroyed. The area of transection must, however, coincide with the transversal distribution of the spinothalamic tract. The extent of this tract in man is not definitely established. It can be said, however, that within the upper segments of the spinal column, fibres within the anterolateral column are more compact and lie more superficially than in the lower segment (*Walker, 1940*). Investigations on cats have shown that on a level with the inferior olive, fibres from the anterolateral column lie assembled within a very limited area (see *e.g. Bohm 1953*). As the spinothalamic tract must be completely transected, the best location for the incision seems to be in the upper cervical region. If the incision is made above the phrenic segment, a certain risk exists for an acute respiratory distress from paralysis of both the diaphragm and the intercostal musculature. A bilateral chordotomy in the upper cervical region must therefore, if possible, be carried out in two sessions. Circulation changes which can result from the first incision must be given a chance to subside, whereupon the risk of an acute paraparesis is diminished at the following session. Under no circumstances should a bilateral chordotomy be performed at the same time if the first incision has produced motor changes.

As a result of the present investigations, the authors wish to suggest that chordotomy, irrespective of the location of pain, should be performed at the cervical level. The greatest advantages are gained in the case of intractable pain localized in the lumbar and lower thoracic segments. The spinothalamic tract within the cervical region occupies a small transversal area and the fibres from the lumbar and sacral segments are superficially located. Therefore the incision needs not to be large and the risk of a postoperative paresis will consequently be smaller since only a portion of the facilitatory system necessary for motor activity is interrupted.

The operative technique perfected during the course of the present investigations appears to result in less complications and gives a more

pronounced analgesia than the thoracic chordotomy (*Bohm*, to be published).

SUMMARY

1. A survey of a material comprising 29 unilateral and 31 bilateral chordotomies is presented, with attention to the frequency of postoperative pareses. The bilateral procedure was complicated in about 50 % of the cases by a paraparesis of variable duration. In 3 cases a paresis persisted for 1-4 years after operation. After unilateral chordotomies one case of transitory monoparesis was noted.

2. In experimental investigations upon monkeys it is shown that the activity recorded from the ventral root and elicited by electrical stimulation of the cortex disappears when the anterior half of the spinal column is transected without injury to the lateral pyramidal tracts.

3. The causes of the appearance of postoperative paresis following anterolateral chordotomy is discussed. The authors are of the opinion that in humans paresis appears when a great part of the anterior half of the spinal cord is damaged. A similar assumption would explain why postoperative pareses appear more frequently after bilateral than after unilateral chordotomies.

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